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(54) Title: IDENTIFYING AND MODULATING MOLECULAR PATHWAYS THAT MEDIATE NERVOUS SYSTEM PLASTICITY

(57) Abstract: The present invention provides methods for identifying genes and pathways involved in plasticity. The invention applies some of these methods to identify genes that are differentially regulated in at least a portion of the nervous system of an individual subjected to conditions known to result in altered nervous system plasticity, i.e., dark rearing (DR) or monocular deprivation (MD). The genes are targets for pharmacological agents that modify plasticity. The invention also identifies biological pathways that are enriched in genes that are differentially regulated under conditions known to result in altered nervous system plasticity. The present invention further provides methods and compositions for modifying plasticity in the nervous system of a subject. The invention includes a method for modifying plasticity in the nervous system of a subject comprising administering a plasticity-modifying agent to the subject, wherein the plasticity-enhancing agent modulates a gene or pathway that is differentially regulated in developmental conditions that alter nervous system plasticity (e.g., DR or MD). The methods and compositions may be administered to a subject suffering from damage to the nervous system or from a neuropsychiatric disorder in order to enhance recovery, reorganization, or function of the nervous system. The methods optionally include administering a proteolysis-enhancing agent to the subject.

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IDENTIFYING AND MODULATING MOLECULAR PATHWAYS THAT MEDIATE NERVOUS SYSTEM PLASTICITY

Related Applications

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent application U.S.S.N. 60/792,275, filed April 14, 2006, which is incorporated herein by reference.

Government Support

[0002] This invention was made with Government Support under Grant No. EY014134 awarded by the NIH. The Government has certain rights in the invention.

Background of the Invention

[0003] Diseases and accidents leading to nervous system damage or degeneration are among the leading causes of mortality and morbidity in many countries. For example, approximately 700,000 people suffer a first or recurrent stroke annually in the United States, resulting in over 150,000 deaths. Although stroke represents the most common cause of damage to the central nervous system (CNS), a number of other conditions are also significant causes of functional deficits due to loss of brain tissue, either as a direct consequence of injury, or secondary to events such as swelling. Among these are primary brain tumors, brain metastases, and surgery for these or other conditions.

[0004] Strokes are a result of a sudden disruption of blood flow to a part of the brain and occur when a blood vessel that normally supplies brain tissue either bursts or becomes transiently or permanently blocked, such as by a blood clot (*e.g.*, a thromboembolus) or other embolus or obstruction. The resulting disruption in normal blood flow deprives the affected tissue of needed oxygen and nutrients and can also impair removal of waste products, resulting in damage to, or death of, nervous system cells. Currently the only therapy for ischemic stroke approved by the U.S. Food and Drug Administration (FDA) is infusion of the thrombolytic agent tissue type plasminogen activator (tPA) within a short time window following the causative event. Such thrombolytic therapy was shown to be both safe and beneficial if delivered within 3 hours of the onset of symptoms (NINDS, Tissue plasminogen activator for acute ischemic stroke. The national institute of neurological disorders and stroke RT-PA stroke study group. *N. Engl. J. Med.* 333: 1581-1587, 1995).

[0005] While stroke is the third leading cause of death in industrialized countries, in most cases stroke is not fatal. However, stroke is a major cause of morbidity and a leading cause of serious, long-term disability. About 4.8 million stroke survivors are alive today in the United States, with a much larger total number worldwide. Many of these individuals suffer from functional limitations affecting the senses, motor activity, speech and/or the ability to understand speech, behavior, thought patterns, memory, emotions, or other aspects of cognition. Although functional deficits following stroke may be permanent, in many cases full or partial recovery is possible. The mainstays of treatment are supportive care and rehabilitation therapy, which frequently continues for months or years. Unfortunately, there are no pharmacological agents that have demonstrated efficacy in improving the long-term outcome of stroke.

[0006] Approximately 10,000-12,000 individuals suffer spinal cord injuries (SCI) each year in the United States, bringing the projected prevalence rate in the United States to nearly 280,000 by the year 2014 (DeVivo, M.J., 2002) Improvements in supportive care have greatly increased the survival rate following such injuries, but therapeutic options remain limited, and efforts focus on rehabilitation. Tumors affecting the spinal cord or meninges (either primary tumors or metastases) are also a significant source of morbidity.

[0007] Disorders of the nervous system also have a massive impact on society. Disorders of brain development, such as autism, now afflict about 1 in 166 children. The total number of individuals in the U.S. afflicted with autism, learning disabilities, and similar disorders is estimated to exceed 4 million. Neuropsychiatric disorders such as schizophrenia and bipolar disorders extract a huge cost in lifetime care for afflicted individuals as well as emotional toll on caregivers and families. Neurodevelopmental disorders such as autism are usually treated with behavioral therapies alone, and these strategies have limited success. Similarly, neuropsychiatric disorders such as schizophrenia and bipolar disorder have very limited therapeutic possibilities.

[0008] Thus there is a need in the art for improved treatments, particularly pharmacological treatments, that would enhance recovery following damage to the CNS and/or help improve CNS and cognitive function in neuropsychiatric and neurodevelopmental disorders. Common to a large range of CNS conditions is the concept that they centrally involve the function of synapses and their ability to change (*i.e.*, plasticity). Thus, there is a need for new approaches to the identification of genes, molecules, cell types, and biological pathways that play a role in key nervous system properties such as plasticity and that can be modulated to provide a therapeutic benefit.

Summary of the Invention

[0009] The invention provides a method of identifying a gene involved in plasticity comprising steps of: subjecting an individual to a condition that modifies nervous system plasticity; measuring level or activity of each of a plurality of genes in at least a portion of the individual's nervous system; and identifying one or more genes whose expression or activity is differentially regulated in the portion of the individual's nervous system relative to its expression or activity under alternative conditions. In some embodiments, the condition comprises depriving at least a portion of the individual's nervous system of normal inputs. The method may comprise identifying a biological pathway or process enriched in genes that are differentially regulated in at least a portion of the nervous system of an individual subjected to a plasticity-modifying condition.

[0010] The invention provides genes that are differentially regulated under conditions that modify plasticity. The invention provides biological pathways that are enriched in such genes. The invention identifies a specific cell type, parvalbumin containing interneurons, as being downregulated under conditions that prolong plasticity. Based at least in part on the identification of these genes, pathways, and cell type, the invention provides combinations of plasticity-modifying agents of particular use. For example, in one embodiment an activator of the insulin-like growth factor 1 (IGF1) pathway (*e.g.*, IGF1 or an active peptide fragment thereof; or a modulator of the JAK/STAT pathway, *e.g.*, IFNγ or an HMG-CoA reductase inhibitor such as a statin) are administered to a subject either individually or in a single composition.

[0011] The present invention provides a method for modifying plasticity in the nervous system of a subject comprising the step of: administering a plasticity-modifying agent to a subject in need thereof, wherein the agent is administered either alone or in combination with one or more additional agents in an amount effective to modify nervous system plasticity, wherein the plasticity-modifying agent modulates a gene or pathway that is differentially regulated in at least a portion of the nervous system of an individual subjected to a plasticity-modifying condition. The agent may be administered once, multiple times, and/or continuously. The time may be selected in conjunction with the amount to be effective to modify nervous system plasticity. Exemplary plasticity-modifying condition comprise dark rearing or monocular deprivation.

[0012] The invention includes a method for promoting recovery and/or reorganization in the nervous system of a subject in need of enhancement of recovery and/or reorganization of the nervous system comprising administering a plasticity-modifying agent to the subject, wherein the plasticity-enhancing agent modulates a gene or pathway that is differentially regulated in the nervous system of an individual subjected to a plasticity-modifying condition, *e.g.*, dark-rearing (DR) or monocular deprivation (MD). The agent is administered in an amount effective to promote recovery or reorganization in the nervous system. The agent may be administered once, multiple times, and/or continuously. The time may be selected in conjunction with the amount to be effective to promote nervous system recovery or reorganization. The subject may be in need of recovery or reorganization of the nervous system as a result of ischemic, hemorrhagic, neoplastic, degenerative, traumatic, and/or neurodevelopmental damage to the nervous system. The subject may be in need of reorganization of the nervous system as a result of a neurodevelopmental or neuropsychiatric disorder. The method can include a step of identifying or providing, *e.g.*, diagnosing a subject as having suffered such damage or having a neurodevelopmental or neuropsychiatric disorder. The methods can include a step of identifying or diagnosing the subject as having a reasonable likelihood (*e.g.*, at least a 5% chance, at least a 10%, or at least a 50% chance).

[0013] The methods may also include administering a proteolysis-enhancing agent such as tissue plasminogen activator (tPA), plasmin, or a PAI inhibitor to the nervous system of the subject. A plasticity-modifying agent of the present invention is, in general, distinct from the proteolysis-enhancing agents described herein. The plasticity-modifying agent and the proteolysis-enhancing agent may be administered as part of a single composition or individually. The present invention provides a composition comprising a plasticity-modifying agent and a proteolysis-enhancing agent. The composition(s) can be delivered using a variety of techniques including injection, via infusion pump, from an implantable microchip, or using a polymeric delivery vehicle. The composition(s) can be administered, for example, to one or more subdivisions or areas of the brain, the spinal cord, or to one or more nerves or nerve tracts innervating diverse regions of the body.

[0014] In certain embodiments the composition is administered by implanting into the subject a drug delivery device that releases the plasticity-modifying agent over a period of time at or in the vicinity of a desired location. The desired location can be, for example, an area of ischemic, hemorrhagic, neoplastic, degenerative, traumatic, and/or neurodevelopmental damage in the central or peripheral nervous system, or location in a brain hemisphere opposite to an area of damage. In some embodiments the drug delivery

device comprises a pump. In some embodiments the drug delivery device comprises a biocompatible polymer, *e.g.*, a biodegradable polymer. In some embodiments the polymeric matrix of the drug delivery device comprises a hydrogel. In some embodiments of the invention the composition comprises a plurality of polymeric microparticles or nanoparticles having the plasticity-modifying agent associated therewith (*e.g.*, encapsulated therein, adsorbed thereon, entangled in a polymer network, *etc.*).

[0015] The invention also includes a drug delivery device for implantation into the body of a subject to modify plasticity. In certain embodiments of the invention the device is implanted to promote nervous system reorganization and/or recovery following ischemic, hemorrhagic, neoplastic, traumatic, degenerative, and/or neurodevelopmental damage.

[0016] An inventive device may include a proteolysis-enhancing agent, *e.g.*, a proteolytic agent such as a protease. Alternatively or additionally, a proteolysis-enhancing agent can be administered separately. In certain embodiments the proteolysis-enhancing agent is plasmin, a plasminogen activator, and/or an inhibitor of an endogenous plasminogen activator inhibitor. For example, in certain embodiments, the proteolysis-enhancing agent is tissue plasminogen activator (tPA), *e.g.*, human tPA. In certain embodiments of the invention, the proteolysis-enhancing agent is plasmin. In certain embodiments, the proteolysis-enhancing agent promotes degradation of a component of the extracellular matrix (ECM). In certain embodiments, the proteolytic agent directly or indirectly degrades fibrin.

[0017] Optionally, the plasticity-modifying agent and/or the proteolysis-enhancing agent is covalently attached to a polymer by an optionally cleavable linkage. In some embodiments, one or both of the plasticity-modifying agent and the proteolysis-enhancing agent is delivered in a solution that forms a gel following contact with physiological fluids. The plasticity-modifying agent and, optionally, a proteolysis-enhancing agent may, for example, be delivered in an amount effective to promote structural reorganization of synaptic connections, increase formation of new synaptic connections, increase dendritic spine motility, promote growth of axons and synaptic connections, inhibit at least in part functional and/or structural deterioration or degradation, stabilize synapses, or any combination of the foregoing.

[0018] In certain embodiments the composition comprises one or more neural growth enhancing agents, neurotransmitters or analogs thereof, neurally active growth factors, neural signaling molecules, neurally active small molecules, and neurally active metals. Alternatively or additionally, one or more of these agents can be administered separately, for example, by focal administration to the nervous system or by an alternate route.

[0019] The invention further provides a method of treating a subject in need of enhancement of recovery or reorganization in the nervous system comprising focally administering a composition comprising a plasticity-modifying agent and a proteolysis-enhancing agent to the central or peripheral nervous system of the subject. The subject will typically have suffered nervous system damage as a result of ischemic, hemorrhagic, neoplastic, degenerative, traumatic, and/or neurodevelopmental damage. The invention provides methods of treating a subject in need of enhancement of recovery and/or reorganization in the nervous system comprising administering a plasticity-modifying agent, a proteolysis-enhancing agent, and a neural growth enhancing agent to the subject. One, more than one, or all of the agents can be administered focally to the central or peripheral nervous system. Agents can be administered separately or in a single composition. Any of the methods for administration contemplated herein can be used.

[0020] In any of the inventive methods, the subject may be engaged in a program of rehabilitation designed to promote functional recovery following ischemic, hemorrhagic, neoplastic, traumatic, and/or neurodevelopmental damage to the nervous system, wherein the subject is so engaged during at least part of the time interval during which the agent is administered or during which the agent remains active in the nervous system of the subject.

[0021] In any of the methods described herein, the subject may be engaged in a program of behavioral or cognitive therapy to improve function of the nervous system following from a neurodevelopmental disorder, wherein the subject is so engaged during at least part of the time interval during which the agent is administered or during which the agent remains active in the nervous system of the subject.

[0022] The present invention provides drug delivery devices comprising: a biocompatible polymer and a plasticity-modifying agent, wherein the plasticity-modifying agent agent is released from the polymer in an amount effective to promote structural or functional recovery or reorganization in the nervous system of the subject. The device may comprise a proteolysis-enhancing agent.

[0023] The present invention provides compositions comprising a plasticity-modifying agent and a neural growth enhancing agent, which is optionally selected from among neurotransmitters or analogs thereof, neurally active growth factors, neural signaling molecules, and neurally active small molecules, and neurally active metals. The invention comprises drug delivery devices, *e.g.*, polymer-based drug delivery devices, comprising the composition.

[0024] This application refers to various patents and publications. The contents of all of these are incorporated by reference. In addition, the following publications are incorporated herein by reference: Ausubel, F., (ed.). *Current Protocols in Molecular Biology, Current Protocols in Immunology, Current Protocols in Protein Science,* and *Current Protocols in Cell Biology,* all John Wiley & Sons, N.Y., edition as of July 2002; Sambrook, Russell, and Sambrook, *Molecular Cloning: A Laboratory Manual,* 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, 2001; Kandel, E., Schwartz, J.H., Jessell, T.M., (eds.), *Principles of Neural Science,* 4th ed., McGraw Hill, 2000; Cowan, W.M., Südhof, T.C., and Stevens, C.F., (eds.), *Synapses,* The Johns Hopkins University Press, Baltimore and London, 2001; and Hardman, J., Limbird. E., Gilman, A. (Eds.), Victor, M. and Ropper, A.H., *Adams and Victor's Principles of Neurology,* 7th ed., McGraw Hill, 2000; Grossman, R.I. and Yousem, D.M., *Neuroradiology: The Requisites,* 2nd ed., C.V. Mosby, 2003; Gillen, G. and Burkhardt, A. (eds.), *Stroke Rehabilitation: A Function-Based Approach,* 2nd ed., C.V. Mosby, 2004; Somers, M.F., *Spinal Cord Injury: Functional Rehabilitation,* 2nd ed., Prentice Hall, 2001; *Goodman and Gilman's The Pharmacological Basis of Therapeutics,* 10th Ed., McGraw Hill, 2001 (referred to herein as *Goodman and Gilman*). In the event of a conflict or inconsistency between any of the incorporated references and the instant specification or the understanding of one or ordinary skill in the art, the specification shall control, it being understood that the determination of whether a conflict or inconsistency exists is within the discretion of the inventors and can be made at any time.

[0025] Where ranges of numerical values are stated herein, the endpoints are included within the range unless otherwise stated or otherwise evident from the context. Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in or excluded from the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

[0026] This application refers to various genes and proteins using names that are well known in the art. At times one or more identifiers and/or accession numbers for these genes

and proteins are provided. Such names, identifiers, and/or accession numbers are utilized in various databases available to one of skill in the art such as Genbank and Pubmed. For example, one of skill in the art can search the Entrez Gene database provided by the National Center for Biotechnology Information (NCBI), available at the web site having URL www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=gene and can thereby locate the Gene ID for any particular gene or protein of interest. The Gene ID entry provides biological information, alternate names, chromosomal location, *etc.*, as well as links to database entries for the corresponding nucleotide and protein sequences and references in the scientific literature. It will be appreciated that the names and/or sequences of genes mentioned herein may differ in different species. The invention encompasses the genes regardless of species. When the methods for modifying plasticity, nervous system structure or function, nervous system recovery or reorganization, *etc.*, are applied to a subject it may be preferable to employ agents that modulate the expression and/or activity of genes and/or pathways as they exist in the species to which the subject belongs, although in many cases such agents will be effective in multiple species. In certain embodiments of the invention the gene is a human gene. One of skill in the art will be able to identify the human homologs of mouse genes mentioned herein in other species such as humans.

Brief Description of the Drawing

[0027] *Figure 1*: Analysis and characterization of genes activated in different paradigms of visual input deprivation. (A) Three experimental groups were considered: control mice, dark-reared (DR) mice and monocularly-deprived (MD) mice. From each sample, tissue from anatomically defined primary visual cortex (V1) was taken at P27. For control and DR mice, V1 was taken from both hemispheres, while for MD mice only V1 contralateral to the deprived eye was used. For each sample, total RNA was extracted and processed for the microarray procedure. MD and DR samples were compared to the control independently, each with two different computational methods (see Example 1): the Significance Analysis of Microarrays (SAM) for analysis of single genes, and gene set enrichment analysis (GSEA). Each procedure identified single genes or gene sets that were up- or down-regulated in deprived groups versus control. This led to the identification of cellular events involved in the two models of input deprivation. (B, C) Comparison of gene expression in (B) dark-reared versus control and (C) monocularly deprived versus control animals, showing the expression levels of all probes. Genes showing significantly different expression levels ($p \leq$

0.01) are shown in red (overexpression in deprivation protocol) or in green (overexpression in control). Gene expression is shown on a logarithmic scale. The dashed white line corresponds to identity (y=x). (D) Heat map showing the levels of expression of representative genes that showed differential expression among those selected for our analysis ($p \leq 0.01$). Each column corresponds to a separate sample (n=6 for MD, n=3 for DR and n=3 for control). High levels of expression correspond to brilliant red, low levels of expression correspond to dark blue (see bottom of the figure for color scale). For each group, 25 randomly chosen genes among the significant genes are shown here. Genes within each group are sorted based on their expression values.

[0028] *Figure 2*: Regulation of genes involved in excitatory and inhibitory transmission in MD and DR animals. (A) Numbers of inhibitory/ excitatory receptor genes that are significantly upregulated in MD or DR versus control. (B) Representation of the Microarray Expression Levels (MEL) in control (con), Monocularly Deprived (MD) and Dark Reared (DR) animals of glutamic acid decarboxylase genes (GAD65 and GAD67), the synthetic enzymes for GABA, and different classes of inhibitory neurons. Only the probes for parvalbumin are significantly downregulated in DR, while the other markers are either upregulated or unchanged (star indicates two-tailed t test, $P<0.05$).

[0029] *Figure 3*: Confirmation of selected molecules with RT-PCR. (A) Heat map of the genes confirmed with semi-quantitative PCR. The level of expression is represented in logarithmic scale; red corresponds to maximal expression and blue to minimal expression. The genes are ranked according to their expression level after MD. (B, C) Representation of the fold increase of selected molecules in DR (B) and MD (C) versus control, showing the ratio between DR or MD versus control for Microarray Expression Levels (red) and PCR values (green). A star indicates that the microarray expression of the corresponding gene is significantly upregulated (two-tailed t test $P<0.05$) in DR vs. control or MD versus control.

[0030] *Figure 4*: Gene Set Enrichment Analysis of gene expression after DR and MD. (A) Example analysis of enrichment of the ARF pathway in the MD versus control data set. The hypothesis tested is that the expression of the ARF gene set (n= 19 genes) is enriched in the MD versus control data set. The genes in the dataset are ranked according to a correlation statistic (signal-to-noise ratio); genes up-regulated after MD vs. control appear first while genes up-regulated in control (that is, downregulated in MD vs. control) appear late. The straight lines represent genes in the ranked list that are in the ARF pathway (bottom). The running enrichment score is plotted in the upper graph (top). The peak enrichment score for the ARF pathway in the MD versus control data set is 0.48, leading to a normalized

enrichment score (NES) of 6.8. (B) Heat map of the expression levels of all the probes of the ARF pathway gene set in the MD and control samples. Highest levels of expression correspond to brilliant red, while lowest levels of expression correspond to dark blue. (C) Distribution of normalized enrichment score (NES) values for the DR versus control data set. The arrows highlight two pathways that are particularly enriched in DR and are discussed in the text: the CREB pathway and the Channel Passive Transporter pathway. The insets show the running enrichment scores for these two pathways; the red arrows show the positions of Creb and GluR1 probes respectively. (D) Distribution of NES values in the GSEA analysis for the MD versus control data set. The arrows indicate two pathways discussed in the text which are particularly enriched in MD: the EGF pathway and the IGF1 pathway. For each of these pathways, the insets show the running enrichment score. The red arrows in the insets point to the positions of Stat1 and IGF1-IGFBP5 probes respectively.

[0031] *Figure 5*. Immunohistochemistry for molecules that show increased expression following DR and MD. Immunohistochemistry for selected molecules was performed on coronal slices containing V1 from P27 control, Dark Reared (DR) and Monocularly Deprived (MD) mice. In DR mice, the expression of three proteins: (A) Parvalbumin, (B) GluR1 and (C) Phospho-Creb was examined. The parvalbumin gene is down-regulated in DR versus control and the immunohistochemistry shows a decrease in the number of parvalbumin-positive neurons in DR animals. The histogram on the right shows a significant decrease ($P<0.01$) in the number of parvalbuminergic neurons versus control. GluR1 and P-Creb proteins were over-expressed in visual cortex of DR animals versus control. In MD mice, the expression of (D) activated Stat1 and (E) IGFBP5 was examined. Both proteins are selectively up-regulated in V1 after 15 days of MD relative to control. Bars in the right panels (B-E) show the intensity of the staining in sections of DR or MD and control animals; for all the molecules examined the intensity of staining was significantly higher in the deprived conditions that in controls ($P<0.05$). For each molecule, low magnification pictures (scale bar = 765 μm) and high magnification pictures (scale bar = 100μm) are shown. Arrows in the low magnification pictures demarcate V1.

[0032] *Figure 6*: Application of IGF1 prevents the ocular dominance shift after MD in mouse V1. (A) Left: Mouse brain showing the location of V1 (black region). Right: Ocular dominance index map in mouse V1. The dotted line separates the binocular zone (b) from the monocular zone (m). Scale bar, 1 mm. (B) Histograms of ocular dominance index in the binocular zone of three representative mice. Red line, P27 control mouse; black line, P27 mouse after 7 days of MD; blue line, P30 mouse after 7 days of MD plus IGF1 application

for the same period. The data from each animal typically includes a region within binocular cortex containing over 2000 pixels. (C). Mean ocular dominance indices of the 3 groups of mice. Open circles, mean ocular dominance index of the binocular zone pixels from each animal; filled circles, average value of each group.

[0033] *Figure 7*: Immunohistochemistry for selected markers of the IGF1 pathway. (A) Double staining for IGFBP5 (green) and GAD67 (red) in visual cortex of a P28 mouse. Yellow arrow shows an overlap between the two colors suggesting that IGFBP5 is present in GABAergic neurons; however the presence of cells immunopositive for IGFBP5 but not for GAD67 (green arrow) and vice versa (red arrow) shows that IGFBP5 is present in other cell classes as well. Scale bar= 17 μm. (B) Immunostaining for selected molecules in three different conditions: P28 control (animal reared in normal light conditions), P28 MD (animals monocularly deprived for 4 days), and P28 MD+IGF1 (animals deprived for 4 days and simultaneously injected IP daily with IGF1 solution). In all the MD panels the cortex shown is contralateral to the deprived eye. Bars at right show the staining intensity of each molecule in the different conditions. Scale bar= 70 μm.

Brief Description of the Table Appendix

[0034] The Appendix, which is a part of the instant specification, consists of the following Tables:

[0035] *Table 4* lists genes whose expression is downregulated in visual cortex under conditions of DR.

[0036] *Table 5* lists genes whose expression is upregulated in visual cortex under conditions of DR.

[0037] *Table 6* lists genes whose expression is downregulated in visual cortex under conditions of long term MD.

[0038] *Table 7* lists genes whose expression is upregulated in visual cortex under conditions of long term MD.

[0039] *Table 8* lists genes whose expression is downregulated in visual cortex under conditions of short term MD

[0040] *Table 9* lists genes whose expression is upregulated in visual cortex under conditions of short term MD.

[0041] *Table 10* lists genes that are downregulated in visual cortex under conditions of short term MD in subjects treated with an activator of the IGF1 pathway.

[0042] *Table 11* lists genes that are upregulated in visual cortex under conditions of short term MD in subjects treated with an activator of the IGF1 pathway.

Definitions

[0043] *Approximately*: As used herein, the term "approximately" in reference to a number is generally taken to include numbers that fall within a range of 10% in either direction of the number (greater than or less than) unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0044] *Agonist*: As used herein, the term "agonist" generally refers to a substance that can directly interact with (*e.g.*, bind to) a receptor and initiate a physiological or a pharmacological response characteristic of the activity of that receptor, *e.g.*, the activity that is normally induced by interaction of an endogenous positively-acting ligand with the receptor. Substances generally recognized in the literature as agonists of a particular receptor are of use in the methods described herein. The term "agonist" also refers to partial agonists, *i.e.*, compounds that are capable of partially activating a receptor, *e.g.*, activating it to a lesser extent than its endogenous ligand. The term also encompasses substances that indirectly stimulate a receptor, *e.g.*, by inhibiting reuptake or breakdown/metabolism of an endogenous direct agonist and/or by stimulating the production or release of an endogenous direct agonist.

[0045] *Antagonist*: As used herein, the term "antagonist" generally refers to a substance that opposes the receptor- associated responses normally induced by another bioactive agent such as an endogenous positively-acting ligand. Typically, an antagonist binds to a receptor and prevents binding of an endogenous ligand that would normally activate the receptor, or prevents binding of an exogenous agonist to the receptor. The antagonist may or may not induce an effect itself. The activity of a receptor is generally taken to be the activity associated with binding of an endogenous positively-acting ligand. Substances generally recognized in the literature as antagonists of a particular receptor are of use in the methods described herein. The term also encompasses substances that indirectly inhibit a receptor, *e.g.*, by inhibiting reuptake or by stimulating breakdown/metabolism of an endogenous direct agonist and/or by stimulating the production or release of an endogenous direct antagonist.

[0046] *Biocompatible*: A material is considered "biocompatible" if it is substantially non-toxic to the recipient, in the quantities and at the location used, and also does not elicit or

cause a significant deleterious or untoward effect on the recipient's body, *e.g.*, a significant immunological or inflammatory reaction, unacceptable scar tissue formation, *etc.*

[0047] *Biodegradable*: As used herein, the term "biodegradable," refers to a material that is capable of being broken down physically and/or chemically within the body of a subject, *e.g.*, by hydrolysis under physiological conditions, by natural biological processes such as the action of enzymes present within the body, *etc.*, to form smaller chemical species which can be metabolized and/or excreted.

[0048] *Biological information resource*: As used herein, the term "biological information resource" refers to a compilation of reliable information about biochemical species (*e.g.*, genes or their expression products, substrates, cofactors, physiologically important ions or small molecules), biological processes, and optionally, biological pathways, from which it is possible to conveniently determine information such as (i) whether a biochemical species is a component of a particular biological process; (ii) which biochemical species are components of a particular biological process; (iii) which biological processes include a particular biochemical species as a component; (iv) whether a particular biological process includes a particular biochemical species as a component, *etc.* A biological information resource can also include any type of additional biological information. For example, information such as identifiers of compounds known to interact with a biochemical species or known to influence a biological pathway can be included. Names of diseases or clinical conditions that are related to a biological process or biochemical species, *e.g.*, in which the biological process or biochemical species plays a causative role, or in which a defect in the biological process or biochemical species plays a causative role, can be included. By "reliable information" is meant information that is generally recognized in the art as being substantially accurate. Typically such information will have been published in the scientific literature and described therein in sufficient detail to be capable of being independently verified and will have been replicated and/or acknowledged as being accurate in one or more additional scientific publications. A biological information resource will typically comprise a database and will provide one or more software tools that allow a user to readily obtain access to the information and to search the information using one or more query terms, *e.g.*,. an identifier for a biochemical species, biological process, *etc.* An "identifier" refers to any term or combination of terms that is used to refer to a biochemical species, biological process, *etc.* The identifier can be, for example, the name of a gene or the name of a biological process.

[0049] *Biological pathway*: As used herein, the term "biological pathway" refers to a sequence of reactions (*e.g.*, physical interactions between molecules, enzyme reactions) that

takes place in a living organism, typically resulting in a biological effect. A pathway typically involves a cascade of events in which molecules involved in the pathway (referred to as "components" of the pathway) signal to or act upon each other, often in a characteristic and ordered manner. Many of the components of the pathway are RNA or polypeptide expression products of genes (also referred to as "gene products"). Such genes may also be referred to as components of the pathway. Biological pathways of interest herein include the IGF1 pathway, the JAK/STAT pathway, the PI3 kinase pathway, and subpathways thereof.

[0050] *Biological process*: As used herein, the term "biological process" refers to a series of events accomplished by one or more biochemical species or ordered assemblies of biochemical species. The biochemical species or assemblies thereof are referred to as "components" of the biological process. The components are said to be "involved in" the biological process. For example, a gene product that is a component of a biological process, *i.e.*, plays a role in carrying out that biological process, is said to be involved in that biological process. Genes whose expression product(s) are components of a biological process may also be referred to as components of the pathway. The series of events making up a biological process is typically directed towards achieving a biological goal of significance to the biological system. Examples of biological processes include, without limitation, cell communication, metabolism, morphogenesis, secretion, *etc.* It will be appreciated that a biological process may comprise a plurality of biological processes (subprocesses). A biological process may comprise or be performed by one or more biological pathways. The "central nervous system" (CNS) includes the brain, spinal cord, optic, olfactory, and auditory systems. The CNS comprises both neurons and glial cells (neuroglia), which are support cells that aid the function of neurons. Oligodendrocytes, astrocytes, and microglia are glial cells within the CNS. Oligodendrocytes myelinate axons in the CNS, while astrocytes contribute to the blood-brain barrier, which separates the CNS from blood proteins and cells, and perform a number of supportive functions for neurons. Microglial cells serve immune system functions.

[0051] *Concurrent administration*: The term "concurrent administration," as used herein with respect to two or more agents, *e.g.*, therapeutic agents, is administration performed using doses and time intervals such that the administered agents are present together within the body, or at a site of action in the body such as in the CNS in amounts sufficient to have a biological effect over a time interval of minutes, hours, days, weeks, *etc.* The agents may, but need not be, administered together as part of a single composition. In addition, the agents may, but need not be, administered simultaneously (*e.g.*, within less than 5 minutes, or within

less than 1 minute) or within a short time of one another (*e.g.*, less than 1 hour, less than 30 minutes, less than 10 minutes, approximately 5 minutes apart).

[0052] *Critical period*: As used herein, the term "critical period" refers to a time period during the development of an organism in which the organism's nervous system is particularly able to acquire a specific functional ability and/or structural configuration, typically at least in part in response to external environmental stimuli. Absence of the appropriate stimuli during the critical period typically results in failure to develop the functional ability and/or structural configuration that would develop had these stimuli been present. The timing and duration of the critical period may depend upon the environmental stimuli received. For example, lack of certain environmental stimuli prolongs the critical period.

[0053] *Deprived condition*: As used herein, the term "deprived condition" refers to an environment that fail to provide adequate environmental stimuli needed to allow normal development of one or more functional or structural features of the nervous system. An individual subjected to a deprivation condition typically receives fewer and/or less intense or varied stimuli of one or more types than an individual subjected to "normal conditions." In the case of an animal raised in a laboratory, "normal conditions" are standard laboratory conditions typically used for the maintenance of such animals.

[0054] *Effective amount*: As used herein, an "effective amount" of an active agent refers to the amount of the active agent sufficient to elicit a desired biological response. As will be appreciated by those of ordinary skill in this art, the absolute amount of a particular agent that is effective may vary depending on such factors as the desired biological endpoint, the agent to be delivered, the target tissue, *etc.* Those of ordinary skill in the art will further understand that an "effective amount" may be administered in a single dose, or may be achieved by administration of multiple doses. A desired biological response may be, for example, (i) functional or structural reorganization of synaptic connections, dendrites, or axon projections; (ii) maintenance of synaptic connections, dendrites, or axon projections under conditions in which they would otherwise deteriorate ; (iii) regeneration of a nerve or an axonal projection system or its maintenance under conditions in which it would otherwise deteriorate; (iv) an improvement in performance of a task requiring motor or sensory function; (v) an improvement in performance of a task requiring cognitive function, *e.g.*, improved performance on a test that measures learning and/or memory; (vi) a slowing in the rate of decline in motor, sensory, and/or cognitive function.

[0055] *Enriched condition*: As used herein, the term "enriched condition" refers to an environment that provides receives more stimuli and/or more intense or varied stimuli of one or more types than an individual subjected to "normal conditions."

[0056] *Expression product*: As used herein, the term "expression product" or "gene product" refers to an RNA transcribed from a gene or a polypeptide translated from an RNA transcribed from a gene. RNAs or polypeptides that are modified following their transcription or translation are considered expression products of the gene that encodes them. Modifications include, *e.g.*, splicing, cleavage, addition of phosphate or fatty acid groups, *etc.*

[0057] *Focal delivery*: As used herein, the term "focal delivery" (or "focal administration" in reference to delivery of a pharmacological agent), refers to delivery that does not rely upon transport of the agent to its intended target tissue via the vascular system, *e.g.*, the agent is not administered directly into a blood vessel. The agent is delivered directly to its intended target tissue or in the vicinity thereof, *e.g.* by injection through a needle, catheter, or cannula, or by implantation of a delivery vehicle or device containing the agent. If the agent is delivered to the vicinity of its target tissue rather than into the target tissue itself, the agent may reach its target tissue by diffusion. For purposes of the present invention, any method that achieves delivery of an agent to the CNS or portion thereof without requiring transport via the vascular system from a site outside the skull or meninges (the membranes that cover the brain and the spinal cord), is considered to achieve focal delivery of the agent. Specifically included are delivery by use of an implanted or external pump, and/or delivery directly into one or more ventricles of the CNS. It will be understood that once having been focally delivered a portion of the agent (typically only a minor fraction thereof) may in part enter the vascular system and be transported to another location.

[0058] *Function*: As used herein, the term "function," with reference to the nervous system or a component thereof, is used broadly herein to refer to any function, role, task, or activity performed by the nervous system or a component thereof. The term includes, without limitation, the ability to process and recall information, regulate behavior, stimulate release of endogenous chemicals, control motor functions, receive and process sensory input, maintain consciousness, *etc.*

[0059] *Functional recovery*: As used herein, the term "functional recovery" refers to the process in which a nervous system or component thereof that has at least in part lost the ability to perform a function that it previously performed, regains at least in part the ability to perform the function. Functional recovery may take place in at least two different ways: (i) the recovery in function may involve partial or complete recovery of the portion of the

nervous system that previously performed the function; (ii) the recovery in function may involve a portion of the nervous system performing a function that it did not previously perform. Of course in some instances both processes may take place. Functional recovery can also refer to preservation of the ability of the nervous system or a portion thereof to perform a function that it previously performed, after the nervous system or component thereof has been physically altered, disrupted, or otherwise subjected to a physical or chemical insult or neurodegenerative disease, when such physical alteration, disruption, physical or chemical insult or neurodegenerative disease would otherwise be expected to lead to deterioration or loss of the ability of the nervous system or portion thereof to perform the function.

[0060] *Functional reorganization*: The term "functional reorganization," as used in reference to the nervous system or a portion thereof, refers to the process in which a portion of the nervous system wholly or partially assumes, *i.e.*, takes on, a function (*e.g.*, a sensory, motor, or cognitive function) that was not previously performed by that portion of the nervous system. The function or task may, but need not have been, previously performed by a different portion of the nervous system. Functional reorganization may, but need not, entail one or more aspects of structural reorganization. Functional reorganization may also be referred to as functional rearrangement.

[0061] An example of functional reorganization is the capacity of an area of sensory or motor cortex adjacent to an area of injury or necrosis of CNS tissue to control CNS output to a portion of the body that was previously controlled by the injured or necrotic tissue, or to receive and process input from a region of the body from which input was previously received and processed by the injured or necrotic tissue. Another example is the capacity of an area of sensory or motor cortex corresponding in location to an area of injury or necrosis of CNS tissue, but located in the opposite hemisphere of the brain, to control CNS output to a portion of the body that was previously controlled by the injured or necrotic tissue, or to receive and process input from a region of the body from which input was previously received and processed by the injured or necrotic tissue. Yet another example is provided by the nervous system's response to monocular deprivation, which is further discussed below.

[0062] *Infarct*: As used herein, the term "infarct" refers to an area of localized tissue necrosis resulting from inadequate blood supply, *e.g.*, due to obstruction of a blood vessel. Also referred to as an infarction. When the necrotic tissue is brain tissue, the infarct may be referred to as a cerebral infarct or cerebral infarction.

[0063] *Modulate*: As used herein, the term "modulate" means to alter, *e.g.*, to increase or enhance, to decrease or inhibit, or to cause a variation in a temporal pattern. To "modulate a gene" means to modulate the level and/or activity of an RNA or polypeptide expression product of the gene, *e.g.*, by administering an agonist or antagonist. "Level" of an expression product refers to amount, *e.g.*, concentration by weight or volume, number of molecules per cell or by weight or volume, *etc.* To "modulate a pathway" means to modulate at least one reaction and/or gene involved in the pathway, typically resulting in an alteration in the biological effect or outcome of the pathway. To "modulate a cell" means to increase or enhance, or to decrease or inhibit, the development, survival, and/or activity of the cell.

[0064] *Neural tissue*: As used herein, the term "neural tissue" refers to one or more components of the central nervous system and/or peripheral nervous system. Such components include brain tissue and nerves, which may be present in bundles or tracts. In general, brain tissue and nerves contain neurons (which typically comprise cell body, axon, and dendrite(s)), glial cells (*e.g.*, astrocytes, oligodendrocytes, and microglia in the CNS; Schwann cells in the PNS). It will be appreciated that brain tissue and nerves typically also contain various noncellular supporting materials such as basal lamina (in the PNS), endoneurium, perineurium, and epineuriun in nerves, *etc.* Additional nonneural cells such as fibroblasts, endothelial cells, macrophages, *etc.*, are typically also present. See Schmidt and Leach, 2003, for further description of the structure of various neural tissues.

[0065] *Peripheral nervous system*: As used herein, the term "peripheral nervous system" (PNS) includes the cranial nerves arising from the brain (other than the optic and olfactory nerves), the spinal nerves arising from the spinal cord, sensory nerve cell bodies, and their processes, *i.e.*, all nervous tissue outside of the CNS. The PNS comprises both neurons and glial cells (neuroglia), which are support cells that aid the function of neurons. Glial cells within the PNS are known as Schwann cells, and serve to myelinate axons by providing a sheath that surrounds the axons. In various embodiments of the invention the methods and compositions described herein are applied to different portions of the PNS.

[0066] *Plasticity*: As used herein, the term "plasticity" refers to the capacity of the nervous system, or a portion thereof, to change (*e.g.*, to reorganize) its structure and/or function, generally in response to an environmental condition, injury, experience, or ongoing nervous system activity. Plasticity may involve the proliferation of neurons or glia, the growth or movement of neuronal processes and/or alterations in their shape. Plasticity may involve formation of new synaptic connections between neurons and/or strengthening or weakening of existing synaptic connections. Formation of new synaptic connections may

involve growth or movement of neuronal processes. Plasticity may also involve alterations in non-neuronal components of the nervous system, *e.g.*, astrocytes or other glial cells.

[0067] *Plasticity-modifying agent*: As used herein, the term "plasticity-modifying agent" refers to a substance whose administration to a subject, either alone or in combination with one or more other substances or non-pharmacological therapy, results in a detectable alteration in the plasticity of at least a portion of the nervous system. The alteration may be evidenced by an alteration in nervous system function and/or structure as compared with the function and/or structure that would be observed in the absence of the agent. The agent has a clinically significant effect on the nervous system to modify plasticity and is not administered simply for nutritional or dietary purposes. The agent may increase, decrease, and/or prolong plasticity.

[0068] *Plurality*: As used herein, the term "plurality" means more than one.

[0069] *Polypeptide*: As used herein, the term "polypeptide" refers to a polymer of amino acids. As used herein, the term "protein" refers to a molecule composed of one or more polypeptides. The terms "protein," "polypeptide," and "peptide" may be used interchangeably herein. Polypeptides as described herein typically contain only natural amino acids, although non-natural amino acids (*i.e.*, compounds that do not occur in nature in polypeptides but that can be incorporated into a polypeptide chain) and/or amino acid analogs as are known in the art may also be employed.

[0070] *Proteolysis*: As used herein, the term "proteolysis" refers to the breakdown, or degradation, of proteins into smaller polypeptides, typically by cleavage of peptide bonds. Ultimately proteolysis may result in breakdown of the protein into individual amino acids.

[0071] *Proteolysis-enhancing agent*: As used herein, the term "proteolysis-enhancing agent" refers to a substance, *e.g.*, a protease, that increases, contributes to, or causes proteolysis of one or more proteins or inhibits an inhibitor of proteolysis.

[0072] *Purified*: As used herein, the term "purified" means separated from many other compounds or entities. A compound or entity may be partially purified, substantially purified, or pure, where it is pure when it is removed from substantially all other compounds or entities (other than solvents, ions, *etc.*), *i.e.*, it is preferably at least about 90%, more preferably at least about 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater than 99% pure. A partially or substantially purified compound or entity may be removed from at least 50%, at least 60%, at least 70%, or at least 80% of the material with which it is naturally found, *e.g.*, cellular material such as cellular proteins and/or nucleic acids. In a preferred embodiment a purified protein is removed from at least 90%, preferably at least 95%, more

preferably at least 99%, or more, of the other proteins in a preparation, so that the purified protein constitutes at least 90%, preferably at least 95%, more preferably at least 99%, of the material in the preparation on a dry w/w basis.

[0073] *Recovery*: As used herein, the term "recovery" refers to structural and/or functional recovery.

[0074] *Reorganization*: As used herein, the term "reorganization" refers to structural and/or functional reorganization.

[0075] *RNAi agent*: As used herein, the term "RNAi agent" refers to a nucleic acid that inhibits gene expression by an RNAi interference mechanism. Examples include short interfering RNAs (siRNAs), short hairpin RNAs (shRNAs), microRNAs (miRNAs) and nucleic acids that are processed intracellularly, *e.g.*, by a member of the RNase III family of nucleases such as DICER that cleaves double-stranded RNAs, to produce an siRNA, shRNA, or miRNA. It will be appreciated that an RNAi agent, if produced using chemical synthesis, can include one or more deoxyribonucleotides or nucleotide analogs, modified backbone structures, *etc.*, in addition to or instead of ribonucleotides linked by phosphodiester bonds.

[0076] *Sequential administration*: As used herein, "sequential administration" of two or more agents refers to administration of two or more agents to a subject such that the agents are not present together in the subject's body at greater than *de minimis* concentrations. Thus the agents are not present together in the subject's body in concentrations sufficient for the agents to each have a separate biological effect. In certain embodiments a first agent is administered to a subject. A second agent is administered at a later time at which the concentration of the first agent has declined to less than 1%, less than 5%, or less than 10% of its peak concentration in the CNS or PNS. Administration of the agents may, but need not, alternate. Each agent may be administered multiple times.

[0077] *Small molecule*: As used herein, the term "small molecule" refers to organic compounds, whether naturally-occurring or artificially created (*e.g.*, via chemical synthesis) that have relatively low molecular weight and that are not proteins, polypeptides, or nucleic acids. Typically, small molecules have a molecular weight of less than about 1500 g/mol. Also, small molecules typically have multiple carbon-carbon bonds.

[0078] *Spine dynamics*: As used herein, the term "spine dynamics" refers to a change in any of various structural properties of spines over time. The properties include spine shape, size, number, density, and motility. Spine dynamics may be examined with respect to the individual spine or with respect to a plurality (*i.e.*,. more than one) of spines.

[0079] *Spine motility*: As used herein, the term "spine motility" refers to a change in spine length over time. When examined with respect to a plurality of spines, spine motility refers to the average change in spine length over time.

[0080] *Structural recovery*: The term "structural recovery," as used in reference to the nervous system or a portion thereof, refers to the partial or complete restoration of a structure that has physically altered, disrupted, or otherwise subjected to a physical or chemical insult, which is intended to include deprivation of oxygen and/or nutrients. "Structural recovery" can also refer to preservation of a structure that has been physically altered, disrupted, or otherwise subjected to a physical or chemical insult, when such physical alteration, disruption, physical or chemical insult would otherwise be expected to lead to deterioration and/or loss or alteration in normal structural features. The structure can be, for example, a synaptic connection, a nerve, nerve bundle, nerve tract, nucleus, brain region, connection between brain regions, *etc.*

[0081] *Structural reorganization*: The term "structural reorganization," as used in reference to the nervous system or a portion thereof, refers to an alteration in the pattern of connections between two or more neurons or between one or more neurons and one or more glial cells (*e.g.*, astrocytes, oligodendrocytes, microglia, Schwann cells) that takes place over a period of time or an alteration in the position of two or more neuronal or glial cell bodies or cell processes (axons, dendrites, dendritic spines) with respect to one another. The alteration may include the formation of synapses between neurons that did not synapse with each other at the beginning of the time period. The alteration may include the formation of additional synapses between neurons that had at least one synaptic connection at the beginning of the time period. The alteration may also or alternatively include loss of synapses that existed at the beginning of the time period. Reorganization may entail growth or retraction of neural processes such as axons (*e.g.*, axonal sprouting or regeneration), dendrites, or dendritic spines, migration of neurons or glia, and/or neuronal or glial cell division. Structural reorganization may also be referred to as structural rearrangement.

[0082] *Subject*: As used herein, the term "subject" or "individual" refers to an individual to whom an agent is to be delivered, *e.g.*, for experimental, diagnostic, and/or therapeutic purposes and/or an individual who is subjected to a condition that modifies plasticity. Preferred subjects are mammals, particularly domesticated mammals (*e.g.*, dogs, cats, *etc.*), primates, or humans.

[0083] *Synapses*: As used herein, the term "synapses" refer to "specialized intercellular junctions between neurons or between neurons and other excitable cells where signals are

propagated from one cell to another with high spatial precision and speed" (De Camilli, in Cowan, *supra*). They are the primary sites of intercellular communication in the mammalian nervous system. In general, the basic structure of a synapse consists of a close juxtaposition of specialized regions of the plasma membrane of two neurons, referred to as the presynaptic and postsynaptic neurons, to form a synaptic junction. The presynaptic neuron is the nerve cell transmitting a signal while the postsynaptic neuron is the recipient of the signal. Most neurons in the vertebrate nervous system possess a cell body and two types of cell processes, axons and dendrites. Signals, *i.e.*, action potentials, are initiated and transmitted by the axon while dendrites (and also the cell body) receive inputs via synaptic contacts from other neurons.

[0084] *Treating*: As used herein, the term "treating" generally refers to medical and/or surgical management of a patient for purposes of bringing about an improvement in the state of a subject with respect to a disease, disorder, or condition from which the subject suffers and/or reducing or slowing further deterioration of the subject's condition. Treating can include reversing, alleviating, and/or inhibiting the progress of, the disease, disorder, or condition to which such term applies, and/or reversing, alleviating, inhibiting the progress one or more symptoms or manifestations of such disease, disorder or condition.

Detailed Description of Certain Embodiments of the Invention

Methods for Identifying Genes, Biological Pathways, and Cells Involved in Plasticity

[0085] The invention provides methods to identify molecular targets (*e.g.*, genes and their expression product(s)) that may be modulated in order to modify plasticity in the nervous system of an individual. The genes are differentially regulated in at least a portion of the nervous system of individuals subjected to a condition that modifies plasticity. For example, in certain embodiments, inventive methods identify a gene wherein the level and/or activity of an expression product of the gene differs in at least a portion of the nervous system of a subject if the subject has been subjected to a condition known to modify plasticity relative to its expression or activity in that portion of the nervous system in a subject who has not been subjected to the condition or who has been subjected to an alternate condition. In some embodiments, inventive methods identify a gene wherein the level and/or activity of an expression product of the gene differs in a portion of the nervous system that has been subjected to a condition that modifies plasticity relative to its expression or activity in a

portion of the nervous system that has not been subjected to a condition that modifies plasticity (*e.g.*, a portion located at a corresponding position of the opposite brain hemisphere of a subject). The portion of the nervous system may be any functionally or structurally defined part, area, region, unit, or component of the nervous system (which terms are used interchangeably herein). Portions of the nervous system include cortex, cerebellum, thalamus, hypothalamus, hippocampus, amygdala, basal ganglia (caudate nucleus, putamen and globus pallidus), midbrain, pons, medulla, nerve tracts, *etc.*, and any sub-portion of the foregoing. For example, subregions of the cortex include visual cortex, auditory cortex, somatosensory cortex, entorhinal cortex, olfactory cortex, Broca's area, Wernicke's area, *etc.* It will be appreciated that these regions themselves may be composed of smaller subregions. For example, the primate cortex has been divided into Brodmann areas 1-49 and 52, some of which include subareas, based on cytoarchitectural distinctions. Important areas of the primate visual cortex are referred to as V1, V2, V3, V4, and MT (also referred to as V5). Portions of the nervous system also include the six major cortical layers (I-VI) and their sublayers. Portions of the nervous system also include cortical columns, a term that refers to collections of cells arranged vertically from the surface of the cortex to the white matter that comprise functional and/or anatomical units. Thus, a cortical column can be defined on the basis of anatomical features (*e.g.* stereotyped patterns of pyramidal cell apical dendrite bundles), functional features (*e.g.* columns of cortical cells all responding to the same stimulus orientation) or both. Cortical columns include ocular dominance, orientation, spatial frequency, and color columns. In certain embodiments, the portion of the nervous system comprises cells of one or more types, *e.g.*, one or more neuronal cell types. Cells may be excitatory or inhibitory. Exemplary cell types found in the nervous system include pyramidal cells, stellate cells, interneurons (*e.g.*, chandelier cells, neurogliaform cells, basket cells, double basket cells, Purkinje cells, granule cells, Cajal-Retzius cells, Meynert cells, *etc.*).

[0086] Inventive methods are applied herein to identify genes that are differentially regulated in the visual cortex under monocular deprivation or dark rearing, both of which are conditions known to modify plasticity. The invention identifies biological pathways enriched in such genes.

[0087] The invention provides a method of identifying a gene involved in plasticity (referred to herein as a "plasticity-related gene") comprising steps of: (i) subjecting an individual to a condition that modifies plasticity; (ii) measuring level or activity of each of a plurality of genes in at least a portion of the individual's nervous system; and (iii) identifying one or more genes whose expression or activity is differentially regulated in the portion of the

individual's nervous system relative to its expression or activity under alternative conditions. Conditions may be environmental conditions that are deficient in one or more environmental stimuli that the individual would normally experience. Conditions may include one or more environmental stimuli that the individual would not normally experience. Alternative conditions may be normal environmental conditions, *e.g.*, standard laboratory conditions. Conditions suitable for maintaining animals are discussed in Guide for the Care and Use of Laboratory Animals, Institute for Laboratory Animal Research (ILAR) Commission on Life Sciences, National Research Council, National Academies Press, Washington, D.C. (1996). It will be appreciated that a range of conditions may be considered "normal" but will generally not include specific efforts to deprive or supplement the nervous system inputs that typically would be received be animal maintained as described in the foregoing reference.

[0088] Inventive methods may include identifying one or more biological processes or pathways involving one or more of the plasticity-related genes. The biological process pathway may be enriched for genes identified by the method. For example, the biological process or pathway may include a higher proportion of genes identified by the method than would be expected based on the number of genes in the process or pathway and the number of known genes in an individual of that particular species. In other words, genes identified as being differentially regulated are over-represented among the genes in the biological process or pathway. See Examples for further details.

[0089] In certain embodiments of the invention, the individual is subjected to the condition during at least a portion of a critical period for development of one or more nervous system structure(s), functions, or properties. Nervous system structures, functions, or properties for which a critical period has been well documented in one or more species include ocular dominance, orientation bias, development of the neuromuscular junction, climbing fiber refinement, whisker barrel map formation, whisker RF tuning, cortical tonotopic map, sound localization, birdsong, and human language. The conditions may include depriving the individual of normal inputs needed for the establishment of any of these structures, functions, or properties. The timing of critical periods and the effects of specific environmental conditions are known in the art (see, *e.g.*, Hensch, 2004, *Annu. Rev. Neurosci.*, 27:549).

[0090] In certain embodiments of the invention, conditions include subjecting a subject to an alteration in visual input, optionally during a critical period for development of the visual cortex. Alteration of visual input during postnatal development causes adaptive changes in the maturation of visual cortex circuitry. One method of use for identifying genes, biological

pathways, and cells involved in activity-dependent plasticity is to alter visual experience during a critical period of development. The timing of such critical periods for development of the visual system is known in the art[4]. One example of altering visual experience is to raise animals in complete darkness from birth (dark rearing). Dark-rearing (DR) has diverse effects on the visual cortex, causing an upregulation of miniature synaptic potentials in subsets of neurons[5], a reduction in spine number together with an increase in area of the spines that remain[6], a change in the threshold for eliciting synaptic potentiation and depression[7,8], and a prolongation of the critical period for eliciting experience dependent changes in visual function[9].

[0091] One example of manipulation of use to study the influence of activity on visual cortex neurons and networks and to identify genes, biological pathways, and cells involved in plasticity is monocular deprivation (MD). In animals with binocular vision, inputs to a portion of the visual cortex become anatomically and functionally segregated into alternating stripes of input from the two eyes, referred to as ocular dominance columns. As a consequence, individual cortical neurons that were originally responsive to both eyes become responsive to only one eye. However, if one eye is deprived of visual input during a critical period (monocular deprivation), that eye loses most of its ability to activate the cortex, and the responses of cells shift towards the nondeprived eye eye, *i.e.*, ocular dominance (OD) shifts in favor of the nondeprived eye. The rapid appearance of the functional deficit is followed by structural changes including a reduction in cortical area driven by the deprived eye and expansion of the area driven by the nondeprived eye, which take place on a timescale of weeks to months. The extent and complexity of thalamocortical axonal arbors from the deprived eye are reduced, while the extent and complexity of arbors from the nondeprived eye increase. MD, which can be achived by suturing the lids of one eye during the critical period, causes an increase in the proportion of neurons in the binocular part of the V1 region of the cortex that respond to the open eye[13]. Short-term MD causes a reorganization of intracortical connections both functionally and structurally[14-17], whereas long-term MD leads in addition to a reduction of thalamocortical arbors from the deprived eye and an expansion of arbors from the non-deprived eye[18,19].

[0092] The individual can be subjected to the condition during all or part of a critical period, *e.g.*, for a total of between 10% and 100% of the critical period. The individual can be subjected to the condition intermittently or continuously. In certain embodiments of the invention the critical period is, *e.g.*, between 24 hours and 1 year in length, *e.g.*, between 24 hours and 60 days in length. The critical period can commence at any time after birth or even

prior to birth and may terminate at any later time, depending upon the particular nervous system structure(s), functions, or properties under consideration.

[0093] Any suitable method can be used to identify the differentially regulated genes. In general, the methods involve obtaining samples of nervous system tissue (*e.g.*, samples of tissue from a portion of the brain such as cortex, hippocampus, *etc.*) from a subject who has been subjected to a condition (*e.g.*, a reduction in or increase in inputs) that modifies plasticity in at least a portion of the nervous system. The level and/or activity of each of a plurality of gene products is measured in the sample and is compared with the level and/or activity that would exist under alternate conditions. The method can involve obtaining a sample of nervous system tissue from a different subject who has not been subjected to the condition or obtaining a sample of nervous system tissue from the same subject but from a portion of the nervous system that has not been subjected to the condition. The level and/or activity in the two samples can be compared in an experiment performed on the two samples. Alternatively or additionally, a comparison with previously gathered data on expression levels and/or activity can be used.

[0094] Methods for determining the level of a gene product are well known in the art, and any suitable method can be used. For example, if the gene product is an RNA, its level can be measured using cDNA or oligonucleotide microarrays, subtractive hybridization, Northern blots, quantitative reverse transcription polymerase chain reaction (RT-PCR), *etc.* If the gene product is a polypeptide, its level can be measured using a variety of immunologically based methods such as immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), Western blot, protein array technology (*e.g.*, antibody arrays or arrays using other specific binding agents, *etc.*).

[0095] Activity of a gene product can also be measured in a variety of ways that will typically depend upon the specific gene product whose activity is being measured. For example, if the gene product is a kinase or phosphatase, the extent to which an endogenous substrate is phosphorylated provides an indication of the activity of the gene product. The substrate is isolated from cell in which it is expressed, and its phosphorylation state is evaluated. Alternatively or additionally, *in vitro* kinase or phosphatase assays can be performed. If the gene product is a transcription factor, an assay that involves measuring expression of a reporter construct that contains a DNA element responsive to the transcription factor can be used. The activity of certain polypeptides is regulated by post-translational modification, localization, and/or physical association (typically noncovalent binding) with one or more cellular structures or molecules. For example, certain polypeptides are activated

or inactivated by phosphorylation. Activity may be assessed using binding assays, assays that determine subcellular localization or association with particular intracellular structures or molecules, assays that determine modification state, electrophoresis, mass spectrometry, *etc.* One of skill in the art will be able to select appropriate methods for determining and comparing the activity of gene products.

[0096] In certain embodiments of the invention a highly parallel method is used. By "highly parallel" is meant that the method determines the level or activity of at least 10 gene products essentially simultaneously and/or in a single experiment. Examples include microarray analysis and protein array analysis, wherein the array comprises at least 10 features (*e.g.*, at least 10 specific binding agents such as oligonucleotides or antibodies are affixed to the array). In certain embodiments of the invention the highly parallel method determines the level or activity of at least 100, at least 1000, at least 10,000, or at least 100,000 gene products essentially simultaneously and/or in a single experiment.

[0097] Many of the genes that have been or will be identified using the above methods are components of one or more biological processes or pathways. Such biological processes or pathways may be identified using a variety of methods. One of skill in the art will be familiar with processes and pathways in which some of the genes play a role or will be able to identify such processes and pathways by searching the literature or by using readily available biological information resources.

[0098] One biological information resource of particular use is the Gene Ontology project (www.geneontology.org). The Gene Ontology (GO) provides a list of three structured, controlled vocabularies (ontologies) that describe gene products and their associated biological processes and cellular constituents using a uniform terminology. In particular, the Gene Ontology database annotates (and thereby associates) identifiers of gene products (*e.g.*, gene names) with identifiers of biological processes of which those gene products are components. The Gene Ontology database can thus be used to identify the gene products that carry out a particular biological process and/or to identify the biological processes in which any gene product of interest plays a role. While the Gene Ontology database is used herein to exemplify the identification of biological processes and pathways that involve genes that are differentially regulated in the nervous system of an individual subjected to a plasticity-modifying condition, any similar compilation of information that associates identifiers of biochemical species with identifiers of biological processes and/or pathways could be used instead of, or in addition to, the Gene Ontology database. For example, the Kyoto Encyclopedia of Genes and Genomes (KEGG) offers somewhat similar facilities. Numerous

additional computer-based resources that provide convenient, unified access to biological information are available on the World Wide Web.

[0099] In certain embodiments, biological processes or pathways whose components (*e.g.*, genes) are over-represented among the plasticity-related genes are identified as likely to be involved in modifying plasticity, *i.e.*, they are identified as plasticity-related processes or pathways. A gene (or other biochemical species) that is a component of a biological process is over-represented among the plasticity-related genes if the likelihood that the number of plasticity-related genes that are associated with that biological process is greater than the number of plasticity-related genes that would be expected to be associated with that biological process based on the number of plasticity-related genes identified and the number of genes that are components of the biological process or pathway. Genes that are components of a biological process or pathway identified as being a plasticity-related process or pathway are candidate plasticity-related genes even if they are not themselves differentially regulated under plasticity-modifying conditions. For example, a first polypeptide that acts as a ligand, receptor, substrate, or binding partner for a second polypeptide whose expression is differentially regulated under plasticity-modifying conditions may be a component of a biological pathway of which the first polypeptide is a component and may be modulated instead of, or in addition to, modulating the first polypeptide.

[00100] In certain embodiments of the invention, once a gene, pathway, or process is identified using the methods described above, its role in nervous system structure(s), functions, or properties is more precisely evaluated using any of a variety of approaches. Certain of these approaches are also useful to modulate plasticity for therapeutic purposes, *e.g.*, to improve recovery or reorganization of the nervous system in a subject in need of recovery or reorganization. For example, an agent that modulates the gene, pathway, or process can be administered to an individual and the effect of the agent on the nervous system is determined. The individual may or may not be subjected to a plasticity-modifying condition such as a deprived or enriched condition. The agent can be administered during all or part of the period of time over which the individual is subjected to the condition. In certain embodiments, a transgenic non-human animal (*e.g.*, a mouse or rat) that has temporally and/or spatially altered expression of the gene (*e.g.*, that lacks or has reduced expression of the gene or has elevated or ectopic expression of the gene) is analyzed to determine whether the animal has altered nervous system structure or function and/or altered plasticity relative to an animal in which expression of the gene is not altered (*e.g.*, a "wild

type" animal). The transgenic animal can be generated using standard methods known in the art and is an aspect of this invention. In certain embodiments, an agent that modulates a gene, pathway, or process that is differentially regulated in individuals subjected to a plasticity-modifying condition is administered to a non-human animal. The animal may or may not be subjected to a plasticity-modifying condition or an event that damages the nervous system. The animal exhibits altered plasticity relative to an animal to which the agent is not administered. The animal is used as a model to screen for additional agents that are useful to alter plasticity and/or promote reorganization or recovery of the nervous system.

[00101] In certain embodiments of the invention, an agent that modulates a gene that is a component of a plasticity-related biological process or pathway is administered. The gene itself may or may not be differentially regulated under a plasticity-modifying condition. In some instances, agents that modulate particular genes, pathways, or pathways will be known to those of skill in the art. Any such agent can be used. In certain embodiments of the invention an RNAi agent such as an siRNA or shRNA is used to inhibit expression of a gene, *e.g.*, by triggering degradation of mRNA transcribed from the gene. RNA-mediated interference (RNAi) has recently emerged as a powerful method to reduce the expression of any target transcript in mammalian cells (see, *e.g.*, Elbashir, 2001; Brummelkamp, 2002; McManus & Sharp, 2002; and U.S. Patent Publications 2005/0026278, 2004/0259248, and 2003/0108923). Briefly, it has been found that the presence within a cell of a short double-stranded RNA molecule referred to as a short interfering RNA (siRNA), one strand of which is substantially complementary to a transcript present in the cell (the target transcript) over a length of about 17-29 nucleotides, results in inhibition of expression of the target transcript. The mechanism typically involves degradation of the transcript by intracellular machinery that cleaves RNA (although translational inhibition can also occur). Short hairpin RNAs are single-stranded RNA molecules that include a stem (formed by self-hybridization of two complementary portions of the RNA) and a loop. The stem-loop structure can be processed intracellularly into an siRNA. In some embodiments, an antibody, aptamer, or other molecule with specific binding properties is used to modulate activity of a polypeptide. In some embodiments, a ligand (*e.g.*, an agonist or antagonist) is used to modulate activity of a receptor. In certain embodiments of the invention, the agent is one that can cross the blood brain barrier so as to achieve an effective concentration in the CNS when administered to the subject at a location outside the nervous system (*e.g.*, orally, intravenously, intraperitoneally) at concentrations that do not cause unacceptable side effects.

[00102] In certain embodiments, antisense oligonucleotides complementary to an mRNA transcript that encodes a polypeptide, or ribozymes that cleave the mRNA transcript, are used to decrease expression. Antisense oligonucleotides, or a vector that provides a template for intracellular synthesis of an antisense oligonucleotide, or cells that synthesize the oligonucleotide, can be administered. Antisense technology and its applications are well known in the art and are described in Phillips, M.I. (ed.) "Antisense Technology," *Methods Enzymol.*, Vol. 313 and 314, Academic Press, San Diego, 2000, and references mentioned therein. See also Crooke, S. (ed.) "Antisense Drug Technology: Principles, Strategies, and Applications" (1^{st} ed), Marcel Dekker, ISBN: 0824705661, 1st edition (2001), and references therein.

[00103] In some embodiments, an aptamer that binds to a polypeptide and inhibits its activity is used. An aptamer is an oligonucleotide (*e.g.*, DNA, RNA, which can include various modified nucleotides, *e.g.*, 2'-O-methyl modified nucleotides) that binds to a particular protein. Aptamers are typically derived from an *in vitro* evolution process (SELEX), and methods for obtaining aptamers specific for a protein of interest are known in the art (see, *e.g.*, Brody, 2000).

[00104] Ribozymes and deoxyribozymes are RNA and DNA molecules that can act as enzymes by folding into a catalytically active structure that is specified by the nucleotide sequence of the molecule. Such molecules have been shown to catalyze the sequence-specific cleavage of RNA molecules. The cleavage site is determined by complementary pairing of nucleotides in the RNA or DNA enzyme with nucleotides in the target RNA. Thus, RNA and DNA enzymes can be designed to cleave to any RNA molecule, thereby increasing its rate of degradation (Cotten and Birnstiel, 1989; Usman, 1996; and Sun, 2000).

[00105] It will be appreciated that synthetic nucleic acids such as siRNA, antisense oligonucleotides, aptamers, ribozymes, *etc.*, can include RNA, DNA, nucleoside analog(s), and/or may included modified sugars, or modified backbone structures.

[00106] Expression or activity of a gene, pathway, or process identified using the methods of the invention can be modulated as described above for purposes of modifying nervous system structure(s), functions, or properties. These approaches are of use to modulate plasticity for therapeutic purposes, *e.g.*, to improve recovery or reorganization of the nervous system in a subject in need of nervous system recovery or reorganization.

[00107] The invention provides methods for modifying plasticity by modulating particular cell types present in the nervous system. Cells present in the nervous system have been classified into a number of different cell types based on their level of expression of a

molecule or portion thereof, or a set of two or more molecules or portions thereof (referred to herein as "markers"). The molecule or portion thereof may be, *e.g.*, a particular gene product, a lipid, a carbohydrate modification of a polypeptide or lipid, *etc.*, (referred to herein as "markers"). The marker(s) are said to be characteristic of the cell type. Cells may be classified into types with varying degrees of specificity. For example, the cell type may be an interneuron or may be more specifically classified as being a particular type of interneuron. Certain cell types may be identified based on their expression of a single marker. Other cell types may be identified based on their expression of two or more markers (referred to as a "set" of markers), in which case each marker may be expressed in more than one cell type with specific sets of markers serving to identify specific cell types. In some instances the cell is identified based on whether or not the marker is detectably present in the cell or at its surface at significant levels (above background). In some instances the cell is identified as being of a particular type based on the level at which the marker is present in the cell relative to the level at which it is present in cells of other types. Markers include molecules and portions thereof, wherein absence of the molecule or portion thereof may in part be used to classify cells into different types. Expression of a marker or a specific set of markers may correlate with various parameters such as morphology (*e.g.*, branching pattern of neuronal processes), location, and/or electrophysiologic properties.

[00108] The invention provides methods for selecting a cell type as a target for modulation to regulate plasticity based on identifying genes that are differentially regulated under plasticity-modifying conditions. Cells of the cell type are involved in regulating one or more aspects of plasticity. Cells of the cell type may play a role in maintaining or terminating a critical period. They may play a role in modifying the ability of other cells to respond to inputs, *e.g.*, nerve impulses arising as a result of environmental stimuli. They may regulate formation of new synaptic connections between neurons and/or regulate the strengthening or weakening of existing synaptic connections. The invention provides methods of selecting a cell type as a target for modulation comprising steps of: (i) subjecting an individual to a condition that modifies plasticity; (ii) measuring level or activity of each of a plurality of genes in at least a portion of the individual's nervous system; (iii) identifying one or more genes whose expression or activity is differentially regulated in the portion of the individual's nervous system relative to its expression or activity under alternative conditions; and (iv) selecting a cell type as a target for modulation, wherein a product of at least one of the genes is a marker of the cell type. "Product" here refers to an expression product of the gene or to a molecule or molecular modification that is present in a cell or at its surface as a result of the

expression of the gene. For example, if the gene encodes a kinase, the "product" may be the phosphorylated form of a substrate of the kinase. In certain embodiments of the invention, the cell type expresses at least two of the differentially regulated genes or expresses at least one of the differentially regulated genes and does not significantly express at least one of the differentially regulated genes. The method may include determining that the number of cells of the cell type is altered in at least a portion of the nervous system of an individual subjected to a plasticity-modifying condition. For example, immunohistochemistry or *in vivo* imaging can be used to evaluate cell number.

[00109] The marker may be any marker recognized in the art as useful to classify cells present in the nervous system into different cell types. In certain embodiments of the invention, the marker is a calcium binding protein. A variety of calcium binding proteins (CBPs) such as calbindin, parvalbumin, and calretenin are recognized in the art as being markers of different types of interneurons (Markram *et al.*, 2004, *Nat. Rev. Neurosci.*, 5:793; and Flames *et al.*, 2005, *Neuron*, 46:377). The marker may be a neuropeptide such as somatostatin, vasoactive intestinal peptide, neuropeptide Y, or cholecystokinin. These neuropeptides are recognized in the art as being markers of different types of interneurons (Markram, 2004; and Flames and Marin, 2005). Certain cell types are identified based on their expression of one or more CBPs and one or more neuropeptides.

[00110] In illustrative embodiments, as described in the Examples, inventive methods are applied to identify the gene that encodes parvalbumin (PV) as being downregulated (underexpressed) in the visual cortex under conditions of DR, which conditions prolong the state of plasticity associated with the critical period. The invention further identifies PV expressing interneurons as being reduced in number in visual cortex under conditions of DR. Thus in certain embodiments of the invention, the cell type selected as a target for modulation is a PV-expressing interneuron, *i.e.*, parvalbumin is a marker of the cell type selected as a target for modulation. In the cortex, interneurons that express PV are inhibitory interneurons that utilize γ-aminobutyric acid (GABA) as their neurotransmitter and are morphologically classifed as basket cells and chandelier cells (Markram, 2004).

[00111] The invention includes computer-readable media (*e.g.*, a hard disk, floppy disk, compact disk, zip disk, flash memory, magnetic memory, *etc.*) that store information related to any of the methods described above. Information may be organized in the form of a database, *i.e.*, a collection of data that is organized so that its contents can easily be accessed, managed and updated. Information may identify one or more genes that are differentially

regulated in at least a portion of the nervous system of an individual subjected to plasticity-modifying conditions, optionally under conditions in which an agent is administered to an individual during or after the time period in which the individual is subjected to plasticity-modifying conditions. Genes can be identified by name, by sequence, by accession number(s), *etc.* It will be appreciated that the information about expression and/or activity may relate to the genes themselves and/or to any of their expression products (RNA or protein). The information may indicate the nature of the conditions under which differential regulation was observed, may identify genes whose expression is altered by a plasticity-modifying agent, *etc.* Genes may be listed in order or ranked, *e.g.*, according to the significance of their differential regulation. Exemplary collections of such information are provided in Tables 4-11. Computer-readable media may store information identifying genes that are not differentially regulated, provided that they also include information pertaining to genes that are differentially regulated and identifies those genes as being relevant to plasticity, to nervous system structure, function, recovery or reorganization, *etc.* Additional information related to the gene(s) and/or to their role in plasticity or nervous system recovery or reorganization can be included, *e.g.*, (i) quantitative information related to the extent to which the gene(s) is/are differentially regulated and/or its significance; (ii) information identifying a biological pathway or process enriched in one or more of the genes; (iii) results obtained by administering an agent that modulates expression or activity of one or more of the genes to a subject, *etc.* The invention also includes methods comprising the step of electronically sending or receiving any of the afore-mentioned information and, optionally, storing at least part of the information and/or creating a new computer-readable medium or copy containing at least part of the information.

Compositions and Methods for Modulating Plasticity and Promoting Nervous System Reorganization and Recovery

[00112] The present invention is based in part on the identification of genes that are differentially regulated in response to particular environmental conditions that modify plasticity, namely dark rearing and monocular deprivation. The invention is based in part on the identification of biological processes and pathways that are enriched for one or more of these differentially regulated genes and are therefore considered herein to be differentially regulated pathways. In some embodiments, the present invention encompasses the recognition that expression products of certain genes that are differentially regulated in

response to DR and/or MD are involved in plasticity. In some embodiments, the present invention encompasses the recognition that certain of these genes are implicated as being involved in structural and/or functional nervous system reorganization following nervous system damage and can be manipulated to achieve therapeutic benefit. In some embodiments, the present invention encompasses the recognition that certain of these expression products, and agents that modulate their expression and/or activity, are of use to promote nervous system recovery and/or reorganization following nervous system damage, *e.g.*, following ischemic, hemorrhagic, neoplastic, degenerative, traumatic, and/or neurodevelopmental damage and/or to inhibit nervous system deterioration that would otherwise occur, *e.g.*, as a result of deprivation of input.

[00113] The invention identifies (i) genes whose expression is downregulated in visual cortex under conditions of DR (Table 4), (ii) genes whose expression is upregulated in visual cortex under conditions of DR (Table 5), (iii) genes whose expression is downregulated in visual cortex under conditions of long term MD (Table 6), (iv) genes whose expression is upregulated in visual cortex under conditions of long term MD (Table 7), (v) genes whose expression is downregulated in visual cortex under conditions of short term MD (Table 8), and (vi) genes whose expression is upregulated in visual cortex under conditions of short term MD (Table 9). The invention identifies genes that are differentially regulated in visual cortex under conditions of short term MD in subjects who are treated with a plasticity-modifying agent, namely an activator of the IGF1 pathway (Tables 10 and 11). These genes are identified as candidates for modulation to modify plasticity and/or to promote functional and/or structural nervous system reorganization or recovery of the nervous system. The genes were identified at least in part by hybridizing mRNA to a microarray from Affymetrix (www.affymetrix.com) that contained probes for a large number of mouse genes (see Example 1). The numbered rows in Tables 4-11 list (from left to right, separated by spaces or tabs) the Affymetrix identifier of the probe, the p value, the data for experimental condition (*e.g.*, MD or DR) and control, the gene symbol corresponding to the probe (where available), accession number(s) for the genes and/or proteins, and Reference Sequence (RefSeq) identifier. Items that are not available or not included are indicated by ---. It will be appreciated that the entries in the tables can be arranged in a number of different ways and the specific ordering presented in the tables is not intended to be limiting. For example, the entries can be listed and/or ranked on the basis of ascending p value, on the basis of the absolute or relative magnitude of the difference in expression between the experimental and control conditions, *etc.*

[00114] One of ordinary skill in the art will be able to obtain additional information about the genes and their expression product(s) listed in Tables 4-11 and/or discussed herein, *e.g.*, their sequences, by searching public databases such as those available through Entrez, the search and retrieval system used at the National Center for Biotechnology Information (www.ncbi.nlm.nih.gov) for databases, including PubMed, Nucleotide and Protein Sequences (*e.g.*, Genbank), Protein Structures, Complete Genomes, Taxonomy, *etc.*, (www. ncbi.nlm.nih.gov/gquery/gquery.fcgi). These databases can be searched using the symbols or names of the genes. One of skill in the art will also recognize that additional information can be found at the publicly available Affymetrix website, Netaffx Analysis Center (www.affymetrix.com/analysis/index.affx), visited April 12, 2006, which allows one to correlate GeneChip® array results with array design and annotation information and can be queried by ID. The website includes libraries for each microarray that provide the IDs of the probes and accession numbers for the corresponding genes and proteins.

[00115] The invention provides methods for modifying plasticity in the nervous system of a subject comprising steps of: administering a plasticity-modifying agent to a subject in need thereof, wherein the agent is administered either alone or in combination with one or more additional agents in an amount effective to modify nervous system plasticity, wherein the plasticity-modifying agent modulates a gene or pathway that is differentially regulated in at least a portion of the nervous system of an individual subjected to a plasticity-modifying condition. In other words, when administered to the subject, the agent modulates a gene or pathway, wherein the gene or pathway is a gene or pathway that is differentially regulated in the nervous system of an individual subjected to a plasticity-modifying condition, *e.g.*, a gene or pathway identified using the methods of the present invention. The subject to whom the agent is administered may or may not be subjected to a plasticity-modifying condition. In certain embodiments of the invention, the plasticity-modifying condition is DR or MD. In certain specific embodiments, the plasticity-modifying condition is MD. In certain embodiments of the invention the agent modifies plasticity in a manner that depends on nervous system activity, *e.g.*, the extent to which the nervous system undergoes structural or functional alteration in the presence of the agent will depend on the type of inputs received by the nervous system and/or the type of stimuli to which the nervous system is subjected. In certain embodiments of the invention, the agent enhances the ability of the nervous system to modify its structure or function in response to the presence of a second agent such as a neural growth enhancing agent. Thus the plasticity-enhancing agent may at least in part play a permissive role, contributing to structural or functional recovery or reorganization in the

nervous system when administered to a subject who is receiving rehabilitative therapy that modifies nervous system inputs or who is receiving a neural growth enhancing agent.

[00116] The invention further provides methods of promoting reorganization or recovery in the nervous system of a subject comprising steps of: administering a plasticity-modifying agent to a subject in need thereof, wherein the agent is administered either alone or in combination with one or more additional agents in an amount effective to promote nervous system reorganization or recovery, wherein the plasticity-modifying agent modulates a gene or pathway that is differentially regulated in at least a portion of the nervous system of an individual subjected to a plasticity-modifying condition, *e.g.*, conditions of DR or MD. The subject may have suffered ischemic, hemorrhagic, neoplastic, traumatic, neurodegenerative, toxic, and/or neurodevelopmental damage to the nervous system. The agent may contribute to (*e.g.*, enhance) recovery or reorganization in the subject's nervous system and/or promote normalization of function. In other words, the degree of reorganization or recovery of the nervous system, or improvement of function, is greater than would have been the case if the agent had not been administered to the subject. In certain embodiments of the invention, the agent does not act solely or primarily by exerting a neuroprotective effect, *e.g.*, does not act solely or primarily by inhibiting cell death or dysfunction (*e.g.*, necrosis or apoptosis). In certain embodiments of the invention, the agent exerts both a neuroprotective effect and a plasticity-enhancing effect. According to certain embodiments of the invention, the agent is capable of exerting a neuroprotective effect but is administered within a particular time window subsequent to a specific damaging event such as a stroke, at a time that falls outside the time window during which the agent would exert a neuroprotective effect.

[00117] The above methods may modify plasticity and/or promote recovery or reorganization in any one or more portions of the nervous system. For example, in certain embodiments of the invention, a method modifies plasticity, *e.g.*, promotes plasticity, and/or promote recovery or reorganization in at least a portion of the visual cortex. In certain embodiments of the invention, the portion of the nervous system is one located in proximity to an implanted drug delivery device. For example, the portion of the nervous system may be located up to 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 centimeters (cm) away from the surface or border of the device.

[00118] Typically, agents and compositions in accordance with the invention promote structural reorganization and/or functional reorganization of the nervous system or a portion thereof or maintain the nervous system in a state in which such reorganization can occur. In certain specific embodiments, agents of the invention promote structural and/or functional

recovery of the nervous system or a portion thereof. It will be appreciated that often there will be a correlation between (i) structural reorganization and/or recovery and (ii) functional reorganization and/or recovery, *e.g.*, both structural reorganization and/or recovery as well as functional reorganization and/or recovery take place. However, in some embodiments of the invention, functional reorganization and/or recovery take place without detectable evidence of structural reorganization and/or recovery. In some embodiments of the invention, structural reorganization and/or recovery take place without detectable evidence of functional reorganization and/or recovery during a particular time period of evaluation. In such embodiments, functional reorganization and/or recovery may occur at a later time, and/or the recovery may not be detected using the particular measurement tools and methods used for the evaluation. It will also be appreciated that reorganization is typically associated with recovery, but reorganization can precede noticeable evidence of recovery, sometimes by a significant period of time.

[00119] Functional recovery from damaging events may involve regrowth of physical connections (*e.g.*, synapses) between surviving nervous system cells (*e.g.*, neurons, glial cells) and/or establishment of new connections. Certain of the plasticity-modifying agents may interact directly with cells (*e.g.*, neurons, glial cells, *etc.*) to enhance their plasticity and/or stimulate their capacity for structural and/or functional reorganization. Agents may be administered in conjuction with an agent that causes degradation of molecule(s) present in the ECM that would otherwise impede beneficial structural changes or would exert inhibitory effects on nervous system cells. In certain embodiments of the invention, two or more agents are administered concurrently or sequentially to a subject. Either or both of the agents may be focally administered to the nervous system of the subject.

Plasticity-Modifying Agents

[00120] The invention identifies a number of genes and biological pathways that may be modulated to modify plasticity. Before discussing certain of these genes and pathways it should be noted that certain of the genes and their encoded polypeptides discussed herein are members of families, and in some cases multiple isoforms of a particular polypeptide exist, as well as post-translationally modified forms (*e.g.*, forms that have been modified by phosphorylation, glycosylation, acylation, *etc.*). In such cases a single name may be used to collectively refer to multiple genes or polypeptides. For example, "PI3K" refers to any member or set of members of the PI3K family. "AKT" refers to at least Akt1, Akt2, and/or Akt3, *etc.* "STAT" refers to at least STAT12, 3, 4, 5a, 5b, 6, and/or7, *etc.* "JAK" refers to at least JAK1, JAK2, JAK3, and/or Tyk2, *etc.* Similarly, the "JAK/STAT pathway" refers to

any pathway involving at least one JAK and at least one STAT. It will be appreciated that in certain embodiments of the invention it will be desirable to selectively modulate one or more members of a family, *e.g.*, one or more members that is/are present in the nervous system. It will be also be appreciated that multiple variant polypeptides encoded by a single gene may arise from RNA and/or protein splicing and that gene editing can also give rise to variants, all of which may be referred to by the same name or symbol herein. The invention thus includes embodiments in which any one or more members of a family, isoforms, splice variants that arise from RNA or protein splicing or gene editing, post-translationally modified forms, *etc.*, are modulated.

[00121] One of ordinary skill in the art will readily understand which particular genes and gene products (*e.g.* mRNA and polypeptides) are referred to using the names listed herein and will be able to retrieve the sequences of these genes and gene products and relevant information such as sources from which the molecule can be purified or obtained using, *e.g.*, publicly available databases such as Genbank and PubMed. For example, one of skill in the art can search the Entrez Gene database provided by the National Center for Biotechnology Information (NCBI), available at the web site having URL www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=gene and can thereby locate the Gene ID for any particular gene or polypeptide of interest. It will be appreciated that allelic variants, homologs, and biologically active fragments or variants of the molecules described herein also be used.

[00122] In some embodiments (described in more detail in the Examples), IGFBP5 is identified as being differentially regulated under a particular deprived condition (MD). IGFBP5 is a component of the IGF1 pathway. The invention contemplates modulating one or more components of the IGF1 pathway in order to modify plasticity. The invention contemplates modulating one or more components of the IGF1 pathway to promote recovery or reorganization of the nervous system in a subject in need thereof.

[00123] As described in the Examples, IGFPB5 is significantly upregulated under conditions of MD in the visual cortex of subjects that are subjected to MD. IGFBP5 is one of the most upregulated genes after MD both at the mRNA and protein level. Furthermore, the IGF1 pathway is one of the biological pathways that is most enriched for genes that are differentially regulated after MD, and both IGFBP5 and IGF1 are constituents of several highly enriched pathways after MD. Therefore, the IGF1 pathway is identified as being a plasticity-related pathway of particular interest. As described in Example 4, administration of an activator of the IFG1 pathway prevented many of the effects of monocular deprivation on

the V1 region of the cortex. To the best of the inventors' knowledge, these results represent the first evidence showing the possible functional involvement of the IGF1/IGFBP5 system in experience-dependent plasticity in the cortex. The results demonstrate that IGF1 and/or pathways and mechanisms involving IGF1 stabilize synapses and alter plasticity.

[00124] IGF1 is a member of a superfamily of growth-promoting peptides related to insulin in sequence and biological activity. The actions of IGF1 are mediated by the type I IGF receptor (IGF1R), which transmits binding of IGF1 to an intracellular signaling cascade. Binding of IGFs to the IGF1R enhances the receptors's tyrosine kinase activity, resulting in phosphorylation of insulin receptor substrates IRS1-IRS4, which leads to activation of two major downstream signaling pathways, the mitogen activated protein kinase (MAPK) and the phosphoinositide 3-kinase (PI3K) pathways. The PI3K pathway is discussed further below. Six IGF binding proteins (IGFBP1-IGFBP6) regulate the biological activity of IGF1 by a variety of mechanisms, and some of the IGFBPs have effects independent of IGF1. IGF1, IGF1R, and certain of the IGFBPs are expressed in the CNS and have been postulated to have a variety of different functions therein (Russo, 2005). IGF1 interacts with a variety of different proteins, and activation of the IGF1 pathway results in phosphorylation of a large number of downstream substrates.

[00125] The IGF1 pathway can be modulated using a variety of different methods. In certain embodiments of the invention, the pathway is modulated so as to increase the activity of the pathway. IGF1 or a biologically active fragment thereof can be administered to the subject to activate the pathway. In some embodiments, the tripeptide GPE is used. Alternatively or additionally, a different ligand of an IGF receptor can be administered. The ligand can be an agonist or antagonist, depending on whether it is desired to inhibit or activate the receptor. In some embodiments, methods include (i) administering agent that disrupts the physical association between IGF1 and an IGFBP; (ii) administering an agent that activates or inhibits a kinase that phosphorylates one or more IGF1 substrates; (iii) administering an agent that activates or inhibits a phosphatase that dephosphorylates one or more IGF1 substrates; (iv) administering an agent that upregulates expression of IGF1 or IGF1R; (v) admininistering an agent that upregulates or downregulates expression of an IGFBP; (vi) administering an agent that increases the expression or activity of a component of the PI3K, and/or Akt signaling cascade. *etc.* In one embodiment, an RNAi agent is used to inhibit expression of one or more genes in the pathway, *e.g.*, a gene encoding an IGF binding protein such as IGFBP5.

[00126] In certain embodiments of the invention, the phosphoinositide 3-kinase (PI3K) signal transduction pathway is modulated. Phosphoinositide 3-kinase, also referred to as phosphatidylinositol 3-kinase, is a lipid kinase and a serine/threonine kinase that is a component of a signal transduction pathway involving Src-like or receptor tyrosine kinases such as the IGF1 receptor. Thus, the PI3K pathway is responsible at least in part for the actions of IGF1. The PI3K kinase superfamily includes a large number of structurally related enzymes with differing regulation and substrates (see Foster, 2003 and Paez *et al.*, 2003, for reviews). "Classical" PI3K comprises a regulatory subunit (p85) and a 110-kDa catalytic subunit (p110). PI3K acts through a downstream effector protein kinase B (PKB, also named Akt) to regulate many cellular processes including cell survival, cell proliferation, vesicular trafficking, inflammation and apoptosis inhibition. Three isoforms of Akt (Akt1, Akt2, and Akt3) are known. When activated, PI3K phosphorylates phosphoinositides at the 3' position of the inositol ring. Following their phosphorylation the phosphoinositides promote Akt activation by phosphorylation. Activated Akt (phosphoAkt) then phosphorylates a variety of substrates.

[00127] As described in the Examples, PI3K, which is activated by IGF1, was significantly diminished in expression after MD, but expression was fully restored after MD when IGF1 treatment was administered, suggesting that the plasticity-related effects of IGF1 may at least in part be mediated through PI3K. The present invention encompasses modulating the PI3K pathway, optionally by modulating the expression or activity of Akt, to modify plasticity in a subject in need thereof. For example, the invention encompasses administering an agent that inhibits or enhances phosphorylation of Akt. The invention contemplates modulating one or more components of the PI3K pathway, *e.g.*, Akt, to promote recovery or reorganization of the nervous system in a subject in need thereof. Agents that modulate activity of PI3K and/or Akt are known in the art (see, *e.g.*, U.S. Patent Publication 2003/0236271, which describes bicyclic or tricyclic fused heteroaryl derivatives useful to inhibit PI3K; and U.S. Patent Publication 2004/0176385, describing small molecule inhibitors of PI3K). In some embodiments, the agent is an RNAi agent, such as an siRNA that is targeted to a component of the PI3K signal transduction pathway (see, *e.g.*, U.S. Patent Publication 2005/0272682).

[00128] In certain embodiments (described in more detail in the Examples), STAT1 is identified as being differentially regulated under a particular deprived condition (monocular deprivation), and the JAK/STAT pathway is identified as being a plasticity-related pathway. In particular, STAT1 is upregulated in the visual cortex of subjects that are subjected to MD.

Furthermore, phosphorylated STAT1 was upregulated, indicating activation of the JAK-STAT cascade. The invention contemplates modulating one or more components of the JAK/STAT pathway in order to modify plasticity in a subject in need thereof. The invention also contemplates modulating one or more components of the JAK/STAT pathway to promote recovery or reorganization of the nervous system in a subject in need thereof. The JAK/STAT pathway is the major signaling mechanism for a diverse group of cytokines and growth factors (reviewed in Rawlings *et al.*, 2004, *J. Cell Sci.*, 117:1281). Binding of these ligands to their receptors induces multimerization of receptor subunits that are associated with Janus tyrosine kinases (JAKs), allowing transphosphorylation of the JAKs. Activated JAKs phosphorylate signal transducers and activators of transcription proteins (STATs), transcription factors that are present in the cytoplasm in latent form until activated. Phosphorylated STATs dimerize and are translocated into the nucleus, where they activate or repress transcription of target genes. In addition to these main components of the JAK/STAT pathway, other proteins that contribute to JAK/STAT signaling include signal-trans adapter molecules (STAMs), STAT-interacting protein (StIP), and the SH2B/Lnk/APS family. There are three main classes of negative regulators of JAK/STAT signaling: suppressor of cytokine signaling (SOCS) proteins, protein inhibitors of activated STATs (PIAS) proteins, and protein tyrosine phosphatases (PTPs).

[00129] The JAK/STAT pathway can be modulated using a variety of different methods. A component of the JAK/STAT pathway (*e.g.*, a STAT or JAK polypeptide), or a ligand of a JAK-binding cytokine receptor can be administered. For example, a receptor agonist can be administered to activate the pathway, or an antagonist can be administered to inhibit the pathway. Other methods to modulate the JAK/STAT pathway include administering an agent that (i) disrupts or inhibits the physical association between a JAK and a STAT; (ii) activates or inhibits a kinase that phosphorylates one or more JAK substrates; (iii) activates or inhibits a phosphatase that dephosphorylates one or more JAK substrates; (iv) upregulates expression of a component of the JAK/STAT pathway; (v) downregulates expression of a component of the JAK/STAT pathway; (vi) disrupts the physical association between a JAK-binding cytokine receptor and a JAK; (vii) activates or inhibits a JAK-binding cytokine receptor; (viii) inhibits or enhances translocation of a STAT to the nucleus; (ix) inhibits association of a STAT with DNA; (x) disrupts the physical association between a JAK-binding cytokine receptor and an endogenous JAK regulating protein such as a SOCS or PIAS protein; (xi) induces or inhibits expression of an endogenous JAK regulating protein, *etc.* As noted above, RNAi agents are of use to inhibit expression of genes in the pathway, *e.g.*, one or more JAK,

STAT, SOCS, or PIAS proteins. In general, inhibiting expression of a JAK or STAT will inhibit the JAK/STAT pathway, while inhibiting expression of a negative regulator such as a SOCS or PIAS protein will activate the pathway.

[00130] The present invention encompasses the discovery that phosphorylated STAT1 is upregulated after MD. Without wishing to be bound by any theory, this upregulation may be a response of the brain to remove or reduce deprived eye connections as well as possibly expand non-deprived eye connections. Thus, upregulating STAT1 or otherwise activating the pathway in which it acts would enhance plasticity and/or increase the ocular dominance shift in a MD model.

[00131] In some embodiments, the agent that modulates the JAK/STAT pathway is a cytokine. Cytokines are polypeptides secreted by immune system cells (*e.g.*, lymphocytes, macrophages, *etc.*) that exert a biological effect on other immune system cells and/or on other cells in the body. Examples include interferons, interleukins, chemokines, *etc.* The cytokine may upregulate a component of the JAK/STAT pathway such as STAT1. IFNγ is an exemplary cytokine of use in the invention to activate the JAK/STAT pathway. In some embodiments, the agent reduces STAT1 expression or activity. Exemplary agents that reduce STAT1 expression or activity include ionomycin and fludarabine. Without wishing to be bound by any theory, administration of these agents may alter the ocular dominance shift in an MD model. In some embodiments, the agent is a peroxisome proliferator receptor (PPAR)-gamma agonist. Examples include various prostoaglandins such as 15-deoxy-delta 12, 14-prostaglandin J(2), thiazolidinediones such as rosiglitazone, *etc.* In certain embodiments of the invention, one or more of these agents is administered to inhibit phosphorylation of one or more STAT or JAK proteins. In some embodiments, the agent is an HMG-CoA reductase inhibitor. HMG-CoA reductase inhibitors include statins such as simvastatin, atorvastatin, lovastatin, *etc.* These agents may be administered to inhibit the JAK/STAT pathway. Agents that inhibit STAT1 phosphorylation by inhibiting JAKs include tryphostins such as AG490 which blocks the action of JAK2 (Meydan *et al.*, 1996, *Nature*, 379:645) and WHI-P131, which blocks the action of JAK3 (Sudbeck *et al.*, 1999, *Clin. Cancer Res.*, 5:1569). Tyrphostins are low molecular weight compounds that specifically inhibit protein tyrosine kinases. See also U.S. Patent 6,080,748, which describes a variety of dimethoxyquinazoline compounds useful as inhibitors of JAK3. See also U.S. Patent Publications 2003/0236244, 2004/0209799, 2004/0097504, 2005/0159385, and 2005/0148574.

[00132] The invention provides methods of modifying plasticity comprising steps of: modulating a cell type characterized in that one or more markers of the cell type is a product of a gene that is differentially regulated in at least a portion of the nervous system of an individual subjected to a condition that modifies plasticity. The invention provides methods of modifying plasticity comprising steps of: modulating a marker of a cell type characterized in that one or more markers of the cell type is a product of a gene that is differentially regulated in at least a portion of the nervous system of an individual subjected to a condition that modifies plasticity.

[00133] As noted above, the invention identifies the gene that encodes PV as being downregulated (*i.e.* underexpressed) in the visual cortex under conditions of DR, which prolong the state of plasticity associated with the critical period. The invention identifies PV expressing interneurons as being reduced in number in visual cortex under conditions of DR. Based at least in part on these discoveries, the invention provides methods of modifying plasticity in the nervous system of a subject comprising administering a plasticity-modifying agent to the subject, wherein the plasticity-modifying agent modulates development, survival, and/or activity of parvalbumin expressing interneurons in at least a portion of the brain. In some embodiments, the agent inhibits development, survival, and/or activity of parvalbumin expressing interneurons in at least a portion of the brain. In certain embodiments of the invention, the plasticity-modifying agent inhibits expression or activity of parvalbumin.

[00134] Exemplary methods of inhibiting development, survival, and/or activity of parvalbumin expressing interneurons include administering L-type calcium channel antagonists such as nimodipine or nifedipine (Jiang *et al.*, 2005, *Neuroscience*, 135:839). In some embodiments, PV expressing interneurons are targeted for elimination by administering a complex comprising a cytotoxic agent and a targeting moiety, wherein the targeting moiety specifically binds to a marker of PV expressing interneurons, *e.g.*, a molecule or portion thereof present at the cell surface of PV expressing interneurons. The complex or a portion thereof may be internalized. The cytotoxic agent selectively kills interneurons that have the marker present at their cell surface. "At the cell surface" is used herein to mean that a molecule or portion thereof is exposed to the extracellular environment and accessible to binding by a suitable binding agent.

[00135] The cytotoxic agent may be covalently or noncovalently associated with the targeting moiety. Alternatively or additionally, both the cytotoxic agent and the targeting moiety may be covalently or noncovalently associated with a third entity. For example, in some embodiments, the cytotoxic agent and the targeting moiety are covalently attached to

one another either directly or via a linker moiety to form a conjugate. In some embodiments, the cytotoxic agent and the targeting moiety are associated with a delivery vehicle such as a polymeric scaffold, polymeric particle, or liposome. A variety of cytotoxic moieties can be used. Exemplary classes include alkalizing or alkylating agents, alkyl sulfonates, aziridines, ethylenimines and methylamelamines, nitrogen mustards, certain antibiotics, anti-metabolites, folic acid analogues, purine analogs, pyrimidine analogs, arabinosides, platinum analogs, microtubule inhibitors (*e.g.*, microtubule depolymerizing agents or stabilizers), topoisomerase inhibitors, proteasome inhibitors, proapoptotic agents, kinase inhibitors, radioisotopes, toxins such as diphtheria toxin, *Pseudomonas* exotoxin A (PE), cholera toxin (CT), pertussis toxin (PT), ricin A chain, botulinum toxin A, conotoxins, *etc.* The marker may be, *e.g.*, an ion channel or receptor subunit that is expressed by PV expressing interneurons. Typically, the marker is present at the cell surface of PV expressing interneurons at a higher average level than the level at which it is present at the cell surface of most or all other cell types in the nervous system. Examples include α subunits of L-type calcium channels (*e.g.*, subunit 1.2 or 1.3; Jiang and Swann, 2005), NR2A subunits of NMDA receptors (Kinney, 2006), and the following ion channel subunits: HCN2, Kv3.1, Kv1.2, Kv1.6, Kv1.1, Kv3.2, HCN1, KVβ1, and Caα1A (Markram, 2004). The targeting moiety can be ligand of a receptor or channel that includes any of the foregoing subunits, an antibody or other specific binding agent (*e.g.*, an aptamer or a binding peptide selected through phage display) that binds to a marker such as any of the foregoing subunits, *etc.*

[00136] Alternatively or additionally, in certain embodiments of the invention, it is desirable to reduce plasticity by accelerating or enhancing the development, survival, and/or activity of PV expressing interneurons. For example, agonists of L-type calcium channels such as BayK 8644 can be used.

[00137] In some embodiments, the present invention relates to administering combinations of multiple plasticity-modifying agents to a subject. The agents may be administered together in a single composition or separately. In some embodiments, an agent that modulates the IGF1 pathway and an agent that modulates the JAK/STAT pathway are administered. In some embodiments, an agent that modulates the IGF1 or JAK/STAT pathway and that inhibits development, survival, and/or activity PV expressing interneurons is administered. In some embodiments, an agent that modulates the IGF1 pathway, an agent that modulates the JAK/STAT pathway, and an agent that inhibits development, survival, and/or activity PV expressing interneurons are administered.

[00138] In some embodiments, the invention relates to compositions comprising multiple plasticity-modifying agents. One such composition comprises an agent that activates the IGF1 pathway and an agent that activates or inhibits the JAK/STAT pathway. The composition can comprise any agent that activates the IGF1 pathway and any agent that activates or inhibits the JAK/STAT pathway. In some embodiments, the composition comprises IGF1 or a biologically active variant or fragment thereof such as GPE, and an HMG-CoA reductase inhibitor such as a statin. In some embodiments, the composition comprises IFNγ or a biologically active fragment or variant thereof and an HMG-CoA reductase inhibitor.

Combined Administration of Plasticity-Modifying Agent and Proteolysis-Enhancing Agent

[00139] In certain embodiments of the invention, one or more plasticity-modifying agents and one or more proteolysis-enhancing agents are administered to a subject. As described in co-pending patent application U.S.S.N. 11/205,501, entitled COMPOSITIONS AND METHODS FOR ENHANCING STRUCTURAL AND FUNCTIONAL NERVOUS SYSTEM REORGANIZATION, now published as U.S. Patent Publication 2006/0104969, the inventors have shown that focal administration of proteolysis-enhancing agents such as tPA, plasmin, or agents with plasmin-like activity to the nervous system of a subject promotes reorganization and recovery in the subject's nervous system. The invention provides methods for modifying plasticity in the nervous system of a subject comprising the step of: administering a plasticity-modifying agent and a proteolysis-enhancing agent to a subject in need thereof, wherein the agents are administered in an amount and for a time effective to modify nervous system plasticity, wherein the plasticity-modifying agent modulates a gene or pathway that is differentially regulated in at least a portion of the nervous system of an individual subjected to a plasticity-modifying condition. For example, in certain embodiments of the invention, the agent modulates a gene or pathway that is differentially regulated in at least a portion of the nervous system of an individual subjected to conditions of dark rearing (DR) or monocular deprivation (MD). The plasticity-modifying agent can be , *e.g.*, any of the agents described herein.

[00140] Without wishing to be bound by any theory, proteolysis of one or more ECM component(s), mediated by a proteolysis-enhancing agent such as tPA and/or plasmin, creates an environment that is permissive for structural reorganization and may enhance activity of a plasticity-modifying agent. Thus, the present invention encompasses the recognition that

enhancing proteolytic activity in the nervous system following nervous system damage in combination with administering a plasticity-modifying agent may permit increased structural remodeling relative to either therapy alone, thereby contributing to improved functional recovery. The following sections describe proteolysis-enhancing agents of use in the invention, drug delivery devices, methods and locations for the focal administration of plasticity-promoting agents and proteolysis-enhancing agents, and various other features of the invention.

[00141] A variety of different proteolysis-enhancing agents, or combinations thereof, are of use in the invention. In certain embodiments of the invention, the proteolysis-enhancing agent is a polypeptide. In certain embodiments of the invention, the polypeptide is a protease. In certain embodiments of the invention, the proteolysis-enhancing agent enhances proteolysis of fibrin. The agent may directly cleave fibrin or may activate an endogenous protease that cleaves fibrin. In certain embodiments of the invention, the agent enhances proteolysis of a component of the ECM other than fibrin in addition to, or instead of, enhancig proteolysis of fibrin. For example, the proteolysis-enhancing agent may cleave one or more extracellular matrix components including, but not limited to, collagen, laminin, fibronectin, and proteoglycans. It is noted that the classification of a particular agent as a plasticity-promoting agent or a proteolysis-enhancing agent should not be understood to be limiting in any way. Thus the effect(s) of the proteolysis-enhancing agent on the nervous system may result wholly or in part from one or more activities that does not involve proteolysis. While the plasticity-promoting agents of the present invention are not recognized as having proteolytic activity, such activity is not excluded, and the effect(s) of the plasticity-promoting agent on the nervous system may result wholly or in part from proteolysis that occurs as an indirect effect of their administration. For example, administration of the plasticity-promoting agent may increase expression of an endogenous proteolysis-enhancing agent such as plasmin or inhibit the expression of an endogenous inhibitor of a proteolysis-enhancing agent.

[00142] Suitable agents for use in the present invention include components of the tPA/plasmin cascade. Components of the tPA/plasmin cascade include plasminogen activators such as tissue plasminogen activator (tPA) and variants thereof, plasminogen, and plasmin. Plasminogen activators (PAs) are serine proteases that catalyze the conversion of plasminogen to plasmin (Vassalli, 1991) by cleavage of a single peptide bond (R561-V562) yielding two chains that remain connected by two disulfide bridges (Higgins and Bennett, 1990). Plasmin is a potent serine protease whose major substrate *in vivo* is fibrin, the

proteinaceous component of blood clots. Plasminogen activation by tPA is stimulated in the presence of fibrin. Plasmin has a broad substrate range and is capable of either directly or indirectly cleaving many other proteins, including most proteins found in the ECM. "Direct," as used herein, means that the protease physically interacts with the polypeptide that is cleaved, while "indirect" means that the protease does not usually physically interact with the polypeptide that is cleaved, but tends to interact with another molecule, *e.g.*, another protease, which in turn directly or indirectly cleaves the polypeptide. Plasmin is also capable of activating metalloprotease precursors. Metalloproteases in turn degrade ECM molecules. Metalloproteases are of use in certain embodiments of the present invention. In addition to the aforementioned substrates, plasmin cleaves and activates various growth factors and growth factor precursors. Although the liver is the major site of plasmin synthesis, plasminogen mRNA and protein have been detected in numerous brain regions. Thus, plasminogen is available to be cleaved by tPA administered to the nervous system.

[00143] Two PAs, tissue-type PA (tPA) and urokinase-type PA (uPA) have been identified in mammals. A major physiological function of PAs to trigger the lysis of clots by activating plasminogen to plasmin, which degrades fibrin. In the body, PA activity is regulated in part by various endogenous serine protease inhibitors that inhibit PAs, a number of which have been identified. Neuroserpin (Gene ID 5274) belongs to the serpin family of the serine protease inhibitors and is expressed by neurons of both the developing and the adult nervous system. Neuroserpin is present in regions of the brain where either tPA message or tPA protein are found, suggesting that neuroserpin may be the selective inhibitor of tPA in the CNS. Plasminogen activator inhibitor 1 (PAI-1; Gene ID 5054) is the main plasminogen activator inhibitor (PAI) in plasma but is also found in the nervous system. Protease-nexin I (Gene ID 5270), PAI-2 (Gene ID 5055), and PAI-3 (Gene ID 268591, *Mus musculus*) are other endogenous PAIs. Protease-nexin I and neuroserpin inhibit plasmin in addition to PAs.

[00144] While not wishing to be bound by any theory, there are a number of potential substrates for tPA and/or plasmin whose proteolysis may contribute to structural reorganization in the nervous system. Among these are various ECM proteins such as fibrin, fibronectin, tenascin, and laminin. In addition to plasmin, tPA may activate other proteases such as the plasmin-like protein hepatocyte growth factor (HGF), which may in turn cleave additional substrates.

[00145] tPA for use in the present invention may be from any species, although for administration to humans, it is generally desirable to use human tPA or a variant thereof. tPA and useful variants thereof, including variants with improved properties are described in U.S.

Patents 6,284,247; 6,261,837; 5,869,314; 5,770,426; 5,753,486 5,728,566; 5,728,565; 5,714,372; 5,616,486; 5,612,029; 5,587,159; 5,520,913; 5,520,911; 5,411,871; 5,385,732; 5,262,170; 5,185,259; 5,108,901; 4,766,075; 4,853,330, and other patents assigned to Genentech, Inc. (see also Higgins 1990). For example, and without limitation, the tPA variant may have an alteration in the protease domain, relative to naturally occurring tPA, and/or may have a deletion of one or more amino acids at the N-terminus, relative to naturally occurring tPA. The tPA variant may have one or more additional glycosylation sites relative to naturally occurring tPA and/or may have an alteration that disrupts glycosylation that would normally occur in naturally occurring tPA when expressed in eukaryotic cells, *e.g.*, mammalian cells. Properties that may be of use include, but are not limited to, increased half-life, increased activity, increased affinity or specificity for fibrin, *etc.*

[00146] Human tPA has been assigned Gene ID 5327 in the Entrez Gene database (National Center for Biotechnology Information; NCBI) and the GenBank entry for the full length amino acid, mRNA, and gene sequences are AAA98809, K03021, and NM_000930, respectively. However, it is noted that it may be preferable to use the mature form of tPA, lacking the signal sequence peptide (as described, *e.g.*, in U.S. Patent 4,853,330 and Yelverton 1983) or a variant thereof.

[00147] The chymotrypsin family serine proteases, of which tPA is a member, are normally secreted as single chain proteins and are activated by a proteolytic cleavage at a specific site in the polypeptide chain to produce a two chain form (Renatus, 1997, and references therein). Both the single chain and two chain forms are active towards plasminogen, although the activity of the two-chain form is greater. Plasmin activates single-chain tPA to the two-chain form, thus resulting in a positive feedback loop. The single chain, the two chain form of tPA, and/or combinations thereof, may be used in the present invention.

[00148] tPA and variants thereof are commercially available and have been approved for administration to humans for a variety of conditions. For example alteplase (Activase®, Genentech, South San Francisco, CA) is recombinant human tPA. Reteplase (Retavase®, Rapilysin®; Boehringer Mannheim, Roche Centoror) is a recombinant non-glycosylated form of human tPA in which the molecule has been genetically engineered to contain 355 of the 527 amino acids of the original protein. Tenecteplase (TNKase®, Genentech) is a 527 amino acid glycoprotein derivative of human tPA that differs from

naturally occurring human tPA by having three amino acid substitutions. These substitutions decrease plasma clearance, increase fibrin binding (and thereby increase fibrin specificity), and increase resistance to plasminogen activator inhibitor-1 (PAI-1). Anistreplase (Eminase®, SmithKline Beecham) is a commercially available human tPA.

[00149] Additional plasminogen activators include streptokinase (Streptase®, Kabikinase®) and urokinase (Abbokinase®), both of which are commercially available.

[00150] Alternatively or additionally, proteolysis-enhancing agents of use in the invention include tPA activators such as *Desmodus rotundus* salivary plasminogen activator (DSPA) Desmoteplase (Paion, Germany) which is derived from vampire bat saliva (Liberatore, 2003, and references therein). Four distinct proteases have been characterized and are referred to as *D rotundus* salivary plasminogen activators (DSPAs). Full-length vampire bat plasminogen activator (DSPA1) is the variant most intensively studied and exhibits >72% amino acid sequence identity with human tPA. However, 2 important functional differences are apparent. First, DSPAs exist as single-chain molecules that are not cleaved into 2 chain forms. Second, the catalytic activity of the DSPAs appears to be dependent on a fibrin cofactor. Urokinase plasminogen activators such as rescupase (Saruplase®, Grunenthal), and microplasmin (a cleavage product of plasminogen) are also of use in various embodiments of the invention. Alfimeprase (Nuvelo) is yet another proteolysis-enhancing agent of use in the present invention. Alfimeprase is a recombinantly produced, truncated form of fibrolase, a known directly fibrinolytic zinc metalloproteinase that was first isolated from the venom of the southern copperhead snake (Agkistrodon contortrix contortrix) (Toombs, 2001). These enzymes breaks down fibrin directly. Fibrolase itself is of use in the present invention. Also of use is staphylokinase (Schlott, 1997).

[00151] In some embodiments of the invention plasmin or mini-plasmin is administered instead of, or in addition to, tPA. A variety of other agents that have plasmin-like activity may be used. In general, such substances are able to cleave typical plasmin substrates, such as the synthetic substrate S-2251™ (Chromogenix-Instrumentation Laboratory, Milan, Italy), which is a conveniently assayed chromogenic substrate for plasmin and activated plasminogen. Other agents that have tPA-like activity (*e.g.*, they are able to cleave plasminogen and activate it in a similar manner to tPA) can be used.

[00152] Lumbrokinase is an enzyme or group of enzymes derived from earthworms *Lumbricus rubellus* which has been known for some time (see, *e.g.*, reporting cloning of a gene encoding lumbrokinase, PI239, GenBank Accession No. AF433650; Ge, 2005). Other

fibrinolytic proteases isolated from earthworms are of use (Cho, 2004). Also of use is nattokinase.

[00153] In some embodiments, a variety of fibrinolytic enzymes that have been isolated from various worms, insects, and parasites can be used in accordance with the present invention. For example, destabilase, an enzyme present in the leech, hydrolyzes fibrin cross-links (Zavalova, 1996; Zavalova, 2002).

[00154] In some embodiments of the invention, plasminogen is administered instead of, or in addition to, tPA.

[00155] Instead of, or in addition to, administering a molecule that itself has plasminogen activator activity, plasmin activity, or plasmin-like activity, substances that increase endogenous expression of plasminogen activators or plasmin may be administered. Such substances may act by increasing transcription or translation of the mRNA that encodes the molecule, stabilizes the molecule, *etc.* They include, but are not limited to, brain derived neurotrophic factor (BDNF), transforming growth factor-β (TGF-β), phorbol esters, and retinoic acid.

[00156] A variety of other agents can be administered to enhance protolysis in the central or peripheral nervous system in order to treat nervous system damage due to ischemic, hemorrhagic, neoplastic, traumatic, degenerative, and/or neurodevelopmental conditions. Certain of these agents are administered focally while others are administered using an alternate route of administration, *e.g.*, oral, intravenous, intraperitoneal, intramuscular, intradermal, transdermal, subcutaneous, pulmonary (*e.g.*, by inhalation into the lungs), nasal, *etc.* For example, sulodexide is a fibrinolytic agent that releases cellular tPA and thus is of use to increase tPA activity. In certain embodiments of the invention it is administered orally (Harenberg, 1998). Other agents of use in the invention to inhibit PAI include enalapril (Sakata, 1999) and ampotherin (Parkinnen, 1993).

[00157] Aspirin, which has been reported to stimulate plasmin activity, is of use in the invention (Milwidksy, 1991). In certain embodiments aspirin is not used, or if the subject is receiving aspirin, a different agent is used in addition to aspirin.

[00158] Another strategy that may be used to increase the level of plasminogen activator activity, plasmin activity, or plasmin-like activity is to administer a substance that inhibits one or more of the endogenous inhibitors of tPA or plasmin. Such endogenous inhibitors include PAI-1, PAI-2, PAI-3, and neuroserpin. A plasminogen activator inhibitor will be referred to as a PAI herein. In some embodiments, an inactive form of a PAI, which is

unable to inhibit plasminogen activators, is used (see, *e.g.*, PCT Publication WO 97/39028; and Lawrence *et al.*, 1997, *J. Biol. Chem.*, 272:7676; both of which describe various inactive forms of PAI). Without wishing to be bound by any theory, an inactive form of PAI may compete with an active form and thereby prevent inhibition of tPA. Small molecules and peptides that inhibit one or more PAIs are known in the art and are of use in the present invention. Examples include PAI-039 (Hennan, 2005), ZK4044 (Liang, 2005), tiplaxtinin (Elokdah, 2004), piperazine-based derivatives (Ye, 2004), T-686 (Ohtani, 1996), fendosal (HP129), AR-H029953XX, XR1853, XR5118 and the peptide TVASS (Gils, 2002).

[00159] RNAi may be used to reduce expression of a transcript that encodes an inhibitory protein, *e.g.*, an endogenous PAI. siRNAs or shRNAs targeted to a transcript that encodes an endogenous PAI can be delivered together with a proteolysis-enhancing agent or administered separately. Alternatively or additionally, a vector that provides a template for intracellular synthesis of one or more RNAs that hybridize to each other or self-hybridize to form an siRNA or shRNA that inhibits expression of an inhibitory protein, or cells that synthesize such RNAs, can be administered.

[00160] Antisense oligonucleotides complementary to an mRNA transcript that encodes an inhibitory protein, or ribozymes that cleave the transcript, or vector that provide template for intracellular synthesis of an antisense RNA or ribozyme can also be used to downregulate expression of the inhibitor. In some embodiments of the invention, an aptamer that binds to a PAI and inhibits its inhibitory activity is used. In some embodiments, an RNA or DNA enzyme that cleaves a transcript that encodes a PAI and thus inhibits its inhibitory activity is used.

[00161] In certain embodiments, an antibody or antibody fragment that binds to a PAI is used to inhibit its activity, or any polypeptide having a similar binding specificity, *e.g.*, an affibody. The antibody or antibody fragment can be any immunoglobulin or immunoglobulin-like molecule that binds to an antigen and can be monoclonal or polyclonal.

[00162] Any substance that acts to counteract the effect of a molecule that is inhibitory for activity of a proteolysis-enhancing agent, whether by causing degradation, by sequestering, by reducing expression, or by blocking interaction of the molecule with another molecule or with a cell will be said to counteract the inhibitory molecule and is within the scope and spirit of the invention.

[00163] The present invention encompasses the recognition that enhancing proteolytic activity in the nervous system following nervous system damage may permit increased structural remodeling, thereby contributing to improved functional recovery and will increase

the efficacy of a plasticity-enhancing agent. However, the invention described herein does not require any particular mechanism of action. The invention encompasses use of variants or modified forms of the proteolysis-enhancing agents, wherein the variants or modified forms do not enhance proteolysis. For example, the invention encompasses variants of proteases (*e.g.*, variants having a mutation in an active site region) in which the sequence has been altered, such that the variant is no longer an active proteolytic agent. The invention also encompasses embodiments in which the proteolysis-enhancing agent has been chemically inactivated, such that it no longer enhances proteolysis. Thus in some embodiments of the invention an inactive form of a proteolysis-enhancing agent is focally administered. However, in general, a proteolysis-enhancing agent is active or capable of being activated when used according to the present invention.

[00164] It will be appreciated that various agents have been focally administered to the nervous system of a subject suffering from ischemic, hemorrhagic, neoplastic, traumatic, toxic, neurodegenerative, and/or neurodevelopmental damage to the nervous system, for purposes other than enhancing proteolysis. For example, analgesic agents are commonly administered. Should it be the case that any of such previously administered agents enhance proteolysis, such agent may be explicitly excluded from the present invention or, if used in the present invention, its use in the context of the present invention differs from such previous use. For example, its use in the context of the present invention involves administration to a different location, uses a different administration means, involves administration in combination with a plasticity-modifying agent, and/or employs a different dose and/or time course, *etc.*

[00165] The ability of PAs to trigger the lysis of clots has led to the use of PAs and other plasminogen-activating proteases such as streptokinase as thrombolytic agents for the treatment of myocardial infarction and stroke, as mentioned above. However, studies have suggested that tPA, which is released by neurons following excitotoxicity such as occurs in ischemia, could increase neuronal damage. Furthermore, release or leakage of tPA out of the vascular system and the attendant potential for damage to nervous system tissue, is a recognized hazard of thrombolytic therapy. Thus the invention described herein, which demonstrates that appropriate administration of plasmin and/or plasminogen-activating proteases such as tPA can actually contribute to structural and/or functional nervous system reorganization and recovery, is particularly noteworthy.

[00166] It will be appreciated that various embodiments of the present invention differ from previously reported uses of tPA (*e.g.*, for purposes of thrombolysis) in at least one of the

following ways, which are described in further detail below: (i) administration as described herein is focally directed to the nervous system and does not typically take place via the vascular system; (ii) administration as described herein is typically performed at least 3 hours following the onset of a stroke or other damaging event and typically at least 12 hours or more following the onset of the damaging event; (iii) administration as described herein may occur multiple times (*e.g.*, 2, 3, or more times) following the onset of a damaging event and/or may occur either intermittently or continuously over a prolonged time period following the onset of a damaging event (*e.g.*, over at least 1 week, 4 weeks, 1 month (30 days), 3 months, 6 months, 1 year, 2 years, 3 years, or even longer); (iv) administration as described herein typically does not use doses that would be sufficient to cause effective blood clot lysis at the site of administration when administered using methods that are intended to achieve blood clot lysis.

Variants and Fragments

[00167] It will be appreciated that most proteins can tolerate a certain amount of sequence variation without substantial loss of functional activity, provided that such sequence variation does not affect key residues that are required for such functional activity. The present invention therefore encompasses variants of the plasticity-enhancing or proteolysis-enhancing polypeptides (and other polypeptides disclosed herein), wherein such variants retain a significant amount of biological activity. For example, the fragment can have substantially similar activity (*e.g.*, at least about 10-20% of the relevant activity) to the original polypeptide, at least about 50% of the relevant activity, *etc.* The term "variants" includes fragments, *i.e.*, polypeptides whose sequence is a continuous subset of a polypeptide disclosed herein. Biologically active variants or fragments of certain polypeptides of interest herein are known in the art. The invention contemplates the use of any such variant or fragment. For example, GPE is a biologically active fragment of IGF1 of use in the invention. Specifically encompassed are variants or fragments in which one or more kringle domains of a polypeptide disclosed herein, *e.g.*, plasmin or tPA, is removed. Certain fragments of use in this invention contain a protease domain and, optionally, at least one kringle domain

[00168] As is well known in the art, certain amino acids are generally similar with respect to particular properties and can frequently be substituted for one another in a polypeptide without significantly altering the functional and structural properties of the polypeptide. For example, the variants may contain one or more conservative amino acid substitutions, which may be defined in accordance with Stryer, *Biochemistry*, 3rd ed., 1988. Amino acids in the

following groups possess similar features with respect to side chain properties such as charge, hydrophobicity, aromaticity, *etc.*, and can be substituted for one another in accordance with certain embodiments of the invention: (1) Aliphatic side chains: G, A, V, L, I; (2) Aromatic side chains: F, Y, W; (3) Sulfur-containing side chains: C, M; (4) Aliphatic hydroxyl side chains: S, T; (5) Basic side chains: K, R, H; (6) Acidic amino acids: D, E, N, Q; (7) Cyclic aliphatic side chain: P (P may be considered to fall within group (1)). One of ordinary skill in the art will recognize that other definitions of conservative substitutions can also be used. Amino acid abbreviations used herein are in accordance with common usage in the art.

[00169] The present invention encompasses administration of variants that are at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, or at least 98% identical to one or more of the polypeptides disclosed herein over a number of amino acids equal to at least 50% of the number of amino acids the polypeptide. Percent identity may be calculated by standard methods. For example, the percent identity between first and second polypeptides over a window of evaluation may be computed by aligning the polypeptides, determining the number of polypepties within the window of evaluation that are opposite an identical polypeptides allowing the introduction of gaps to maximize identity, dividing by the total number of amino acid positions in the window, and multiplying by 100. Various computer programs such as BLAST2, BLASTP, Gapped BLAST, *etc.*, generate alignments and provide % identity between sequences of interest. Algorithms employed in those programs (utilizing default values) can be used.

[00170] The present invention encompasses variants in which up to 20%, up to 15%, up to 10%, up to 5%, or up to 2% of the amino acid residues are either substituted (*e.g.*, conservatively substituted), deleted, or added, relative to a polypeptide disclosed herein. Specifically encompassed are allelic variants that exist within a population. The invention encompasses variants that are specifically recognized by immunological reagents (*e.g.*, monoclonal or polyclonal antibodies) that recognize a polypeptide disclosed herein, *i.e.*, the immunological reagent binds to the variant with a substantially similar affinity (*e.g.*, having a K_a at least 50% as great) as that with which it binds to the polypeptide.

[00171] The invention encompasses variants that have a substantially similar overall structure to the polypeptides disclosed herein. For example, certain variants possess sufficient structural similarity to a protein disclosed herein so that when its 3-dimensional structure (either actual or predicted structure) is superimposed on the structure of the protein the volume of overlap is at least 70%, at least 80%, or at least 90% of the total volume of the structure. Furthermore a partial or complete 3-dimensional structure of a variant may be

determined by crystallizing the protein using methods known in the art. Alternatively or additionally, an NMR solution structure can be generated (see, *e.g.*, Heinemann, 2001; Wishart D. 2005; and references therein). A modeling program such as MODELLER (Sali and Blundell, 1993), or any other modelling program, can be used to generate a predicted structure. The PROSPECT-PSPP suite of programs can be used (Guo, 2004).

[00172] In certain embodiments of the invention, the variant has substantially similar plasticity-modifying or proteolysis-enhancing activity as the polypeptide of which it is a variant. In certain embodiments of the invention, the variant does not have a substitution at an active site residue. Active site residues of serine proteases such as the proteases disclosed herein are well known in the art.

Methods of Preparing the Agents of the Invention

[00173] The agents disclosed herein are all known in the art, and it is believed that appropriate methods for their manufacture are well within the skill of those in the art and therefore need not be described here in detail. For example, and without limitation, many of the small molecules described herein can be chemically synthesized using known methods, as can siRNAs and antisense oligonucleotides, and peptides. Certain agents can be purified from natural sources.

[00174] Plasticity-modifying agent such as IGF1, IFNγ, and proteolysis-enhancing agents, *e.g.*,. tPA, or other polypeptides such as plasmin, growth factors, *etc.*, for use in the present invention, may be purified from natural sources, manufactured using recombinant DNA technology (*e.g.*, recombinant tPA), synthesized using purely chemical synthesis (*i.e.*, synthesis not requiring the use of cells to produce the polypeptide), *etc.*

[00175] Methods for producing a polypeptide of interest using recombinant DNA technology are well known in the art. Briefly, such methods generally involve inserting a coding sequence for the polypeptide into an expression vector, operatively associated with expression signals such as a promoter, such that mRNA encoding the protein is transcribed when the expression vector is introduced into a suitable host cell. The host cell translates the mRNA to produce the polypeptide. The polypeptide can include a secretion signal sequence so that the polypeptide is secreted into the medium. The polypeptide may be harvested from the cells or from the medium. Transgenic animals and plants are commonly used to produce

polypeptides. Plants into which viral vectors have been introduced are also used to produce polypeptides.

[00176] Small molecules such as non-peptide neurotransmitters and analogs thereof, small peptides, neurally active metals, and other compounds disclosed herein are typically either purified from natural sources or chemically synthesized, as appropriate, according to standard methods.

[00177] Any of the agents disclosed herein can be provided as pharmaceutically acceptable salts, prodrugs, *etc.* Furthermore, any of the polypeptides disclosed herein can be modified using a variety of methods known in the art. For example, they can be modified by addition of polyethylene glycol (PEG) or variants thereof. Such modifications may increase the active half-life of the polypeptide (see, *e.g.*, Nektar Advanced Pegylation 2005-2006 Product Catalog, Nektar Therapeutics, San Carlos, CA, which describes a number of such modifying agents and provides details of appropriate conjugation procedures). For administration by injection or infusion, compositions of the invention will typically be mixed with pharmaceutically acceptable carriers or diluent such as sodium chloride (*e.g.*, 0.9%) or dextrose (*e.g.*, 5% dextrose) aqueous solutions. Agents can be provided for administration either in solution or in lyophilized or otherwise dried form. They can be reconstituted in water, saline, *etc.*, followed by dilution in an appropriate pharmaceutically acceptable carrier or diluent.

Polymer-Based Drug Delivery Devices

[00178] The invention provides a drug delivery device for implantation into the nervous system of a subject to promote recovery or reorganization, *e.g.*, following ischemic, hemorrhagic, neoplastic, traumatic, and/or neurodevelopmental damage to the nervous system. The drug delivery device comprises a release material, a plasticity-modifying agent, and, optionally, one or more additinoal active agents such as a proteolysis-enhancing agent. The term "release material" is used to refer to any matrix or material that releases incorporated molecules by diffusion or disintegration of the matrix. In certain embodiments of the invention the release material is a biocompatible polymer. The proteolysis-enhancing agent is released from the release material in an amount effective to promote reorganization and/or recovery of the nervous system. A drug delivery device in which an an active agent is physically associated with a polymeric material such as those disclosed herein is referred to as a "polymer-based drug delivery device" in order to distinguish such devices from

mechanical drug delivery devices such as infusion pumps, which are used in various embodiments of this invention, though it should be recognized that materials other than polymers could also be used.

[00179] In certain embodiments of the invention, the plasticity-modifying agent and, optionally, the proteolysis-enhancing agent, is/are incorporated into or otherwise physically associated with a biocompatible polymeric matrix, which may be biodegradable or nonbiodegradable. Any form of physical association is acceptable provided that the association remains stable under conditions of storage and implantation and for sufficient time to release the active agent over a desired time period. For example, the active agent may be encapsulated within a polymeric matrix, entrapped or entangled within a polymeric matrix, adsorbed to the surface of a polymeric matrix, covalently attached to a polymeric matrix, *etc.* The matrix is delivered to or implanted into the body at the location of the target tissue or in the vicinity thereof. The agent is released from the polymeric matrix over a period of time, *e.g.* by diffusion out of the matrix or release into the extracellular environment as the matrix degrades or erodes. In some embodiments, the active agent is incorporated into liposomes.

[00180] The polymeric matrix may have a number of different shapes. For example, microparticles of various sizes (which may also be referred to as beads, microbeads, microspheres, nanoparticles, nanobeads, nanospheres, *etc.*) can be used. Polymeric microparticles and their use for drug delivery are well known in the art. Such particles are tyically approximately spherical in shape but may have irregular shapes. Generally, a microparticle will have a diameter of less than 500 microns, more typically less than 100 microns, and a nanoparticle will have a diameter of 1 micron or less. If the shape of the particle is irregular, then the volume will typically correspond to that of microspheres or nanspheres. Methods for making microspheres are described in the literature, for example, in U.S. Patent 4,272,398; Mathiowitz and Langer, 1987; Mathiowitz *et al.*, 1987; Mathiowitz *et al.*, 1988; Mathiowitz *et al.*, 1990; Mathiowitz *et al.*, 1992; and Benita *et al.*, 1984. Solid nanoparticles or microparticles can be made using any method known in the art including, but not limited to, spray drying, nanoprecipitation, phase separation, single and double emulsion solvent evaporation, solvent extraction, and simple and complex coacervation. Preferred methods include spray drying and the double emulsion process. Solid agent-containing polymeric compositions can also be made using granulation, extrusion, and/or spheronization.

[00181] The conditions used in preparing the particles may be altered to yield particles of a desired size or property (*e.g.*, hydrophobicity, hydrophilicity, external morphology,

"stickiness," shape, *etc.*). The method of preparing the particle and the conditions (*e.g.*, solvent, temperature, concentration, air flow rate, *etc.*) used may also depend on the agent being encapsulated and/or the composition of the polymer matrix. If the particles prepared by any of the above methods have a size range outside of the desired range, the particles can be sized, for example, using a sieve.

[00182] Solid nanoparticles or microparticles can be suspended or dispersed in a pharmaceutically acceptable fluid such as physiological saline and focally administered by injection or infusion (*e.g.*, using a pump) to the nervous system.

[00183] Solid polymer-agent compositions (*e.g.*, discs, wafers, tubes, sheets, rods, *etc.*) can be prepared using any of a variety of methods that are well known in the art. For example, in the case of polymers that have a melting point below the temperature at which the agent is to be delivered and/or at which the polymer degrades or becomes undesirably reactive, a polymer can be melted, mixed with the agent to be delivered, and then solidified by cooling. A solid article can be prepared by solvent casting, in which the polymer is dissolved in a solvent, and the agent is dissolved or dispersed in the polymer solution. Following evaporation of the solvent, the substance is left in the polymeric matrix. This approach generally requires that the polymer is soluble in organic solvent(s) and that the agent is soluble or dispersible in the solvent. In still other methods, a powder of the polymer is mixed with the agent and then compressed to form an implant. Microparticles or nanoparticles comprising a polymeric matrix and a proteolysis-enhancing agent and optionally one or more other active agents can be compressed, optionally with the use of binders, to form an implant.

[00184] A polymeric matrix can be formed into various shapes such as wafers, tubes, discs, rods, sheets, *etc.*, which may have a range of different sizes and volumes. For example, prior to polymerization, a polymer solution may be poured into a mold having the appropriate shape and dimension. Following polymerization the material assumes the shape of the mold and is usable as an implant. The agent(s) may be present in the solution prior to polymerization, or the implant may be impregnated with the agent following its fabrication.

[00185] Suitable biocompatible polymers, a number of which are biodegradable include, for example, poly(lactides), poly(glycolides), poly(lactide-co-glycolides), poly(lactic acids), poly(glycolic acids), poly(lactic acid-co-glycolic acids), polycaprolactone, polycarbonates, polyesteramides, polyanhydrides, poly(amides), poly(amino acids), polyethylene glycol and derivatives thereof, polyorthoesters, polyacetals, polycyanoacrylates, polyetheresters, poly(dioxanones), poly(alkylene alkylates), copolymers of polyethylene glycol and

polyorthoesters, biodegradable polyurethanes. Other polymers include poly(ethers) such as poly(ethylene oxide), poly(ethylene glycol), and poly(tetramethylene oxide); vinyl polymers-poly(acrylates) and poly(methacrylates) such as methyl, ethyl, other alkyl, hydroxyethyl methacrylate, acrylic and methacrylic acids, and others such as poly(vinyl alcohol), poly(vinyl pyrolidone), and poly(vinyl acetate); poly(urethanes); cellulose and its derivatives such as alkyl, hydroxyalkyl, ethers, esters, nitrocellulose, and various cellulose acetates; poly(siloxanes), *etc.* Other polymeric materials include those based on naturally occurring materials such as polysaccharides (*e.g.*, alginate), chitosan, agarose, hyaluronic acid, gelatin, collagen, and/or other proteins, and mixtures and/or modified forms thereof. Chemical derivatives of any of the polymers disclosed herein (*e.g.*, substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art) are encompassed. Furthermore, blends, graft polymers, and copolymers, including block copolymers of any of these polymers can be used. It will be appreciated that a vast number of different polymer variations are available. It will be understood that certain of these polymers require use of appropriate initiators or cross-linking agents in order to polymerize.

[00186] One of skill in the art will understand that in choosing an appropriate polymer and method of manufacture, it is important to select materials and methods that are compatible with stability of the agent. For example, it may be desirable to avoid processing temperatures that are likely to result in substantial degradation or denaturation of the agent, which may result in loss of bioactivity. It will also be desirable to test the composition so as to ensure that the agent is released in significant amounts over the desired period of time.

[00187] In general, the following criteria are important for selection of a material to be used for delivery of the active agent(s): (1) minimal or no cytotoxicity, (2) minimal or no elicitation of immune responses and inflammation, (3) compatibility with aqueous solutions and physiological conditions, and (4) compatibility of the material and its processing methods with the stability of the agent to be incorporated. It may be desirable to utilize a material with a controlled rate of biodegradation. Features such as cross-linking and monomer concentration may be selected to provide a desired rate of degradation and release of the agent. It will be appreciated that a polymeric drug delivery device of the invention may include one or more pharmaceutically acceptable materials such as buffers, spheronizing agents, fillers, surfactants, disintegrants, binders, or coatings. Exemplary materials are described in U.S. Patent 5,846,565.

[00188] Methods for purifying or synthesizing the various polymers for use in drug delivery systems of the invention are known in the art. Methods for incorporating therapeutically active agents into polymeric matrices are likewise known in the art. For example, the active agent can be combined in solution with the polymer prior to polymerization or can be provided in solid form and encapsulated as the polymer polymerizes. A number of different agents have been delivered to the CNS using such polymer matrices. For example, chemotherapeutic agents have been delivered to tumors in the nervous system by encapsulating the agent in a polymeric matrix, which is made into a shaped form, and surgically implanting the matrix into the brain (see, *e.g.*, U.S. Patents 5,626,862; 5,651,986; and 5,846,565). Additional drug delivery devices in which an active agents is provided in a polymeric matrix are described (see, *e.g.*, U.S. Patents 4,346,709 and 5,330,768; Wu, 1994; Dang, 1996; Fleming, 2002; and Westphal, 2002).

[00189] Similar methods to those used in the afore-mentioned references are of use to focally deliver the agents of the invention. In certain embodiments of the invention, the drug delivery device provides controlled or sustained release, *i.e.*, the proteolysis-enhancing agent and any other agents contained in the device are released over a prolonged period of time, *e.g.*, hours to days, weeks, or months.

[00190] Preparation of polymer-agent drug delivery devices can be performed using standard methods known in the art. Briefly, drug delivery devices are typically prepared in one of several ways. For example, the polymer can be melted, mixed with the substance to be delivered, and then solidified by cooling. Such melt fabrication processes generaly utilize polymers having a melting point that is below the temperature at which the substance to be delivered and the polymer itself degrade or become reactive. Alternatively or additionally, the device can be prepared by solvent casting, where the polymer is dissolved in a solvent, and the substance to be delivered dissolved or dispersed in the polymer solution. The solvent is then evaporated, leaving the substance in the polymeric matrix. Solvent casting typically utilizes a polymer that is soluble in organic solvents, and the drug to be encapsulated should be soluble or dispersible in the solvent. Similar devices can be made by phase separation or emulsification or even spray drying techniques. In still other methods, a powder of the polymer is mixed with the agent and then compressed to form an implant.

[00191] Methods of producing implants also include granulation, extrusion, and spheronization. A dry powder blend is produced including the desired excipients and microspheres. The dry powder is granulated with water or other non-solvents for microspheres such as oils and passed through an extruder forming "strings" or "fibers" of wet

massed material as it passes through the extruder screen. The extrudate strings are placed in a spheronizer which forms spherical particles by breakage of the strings and repeated contact between the particles, the spheronizer walls and the rotating spheroniter base plate. The implants are dried and screened to remove aggregates and fines.

[00192] These methods can be used to make microimplants (microparticles, microspheres, and microcapsules encapsulating drug to be released), slabs or sheets, films, tubes, and other structures. A preferred form for infusion or injection is microimplants, as described elsewhere herein.

[00193] Proteins and peptides have been successfully incorporated into polymeric matrices. For example, insulin has been incorporated into biodegradable polymeric microcapsules and retains essentially the same bioactivity as the free form (Takenaga 2004). Natural and synthetic collagenous matrices have been used as carriers of a variety of different growth factors (Kanematsu, 2004).

[00194] Of particular interest in the present invention are polymers that form hydrogels, *i.e.*, gels that contain a substantial proportion of water. Hydrogels may, for example contain 30%, 40%, 50%, 60%, 70%, 80%, 90%, or an even greater amount of water on a w/w basis. Polymeric materials can be formed into hydrogels either prior to or following administration to a subject. An exemplary material comprises hPLA-b-PEG-PLA macromers. The agent is mixed with the polymer solution prior to initiating polymerization. Other suitable hydrogel-forming polymers are known in the art. For example, a variety of polysaccharides, polypeptides, and derivatives thereof can be used. Exemplary polysaccharides include alginate, collagen, cellulose, hyaluronic acid, dextran, chitosan, derivatives of any of the foregoing, *etc.* Other materials that form hydrogels include synthetic polymers such as polyethylene oxide-polypropylene glycol block copolymers such as Pluronics™ or Tetronics™, poly(vinyl alcohol), silicones, polypeptides such as gelatin, polyethylene glycol and related molecules, polyethylene oxide and related molecules or derivatives, *etc.* The hydrogel precursor materials may contain or be modified to contain functional groups that become crosslinked to one another. Optionally, photopolymerization is employed. In some embodiments, a drug delivery device comprising biodegradable macromers such as those described in U.S. Patent 6,153,211 is used.

[00195] In some embodiments of the invention, a plasticity-modifying agent, a proteolysis-enhancing agent, or both, is covalently attached to the polymer, optionally via a moiety that is cleavable *in vivo*, such as an ester linkage or disulfide bond.

[00196] The polymer-based drug delivery devices of the invention may be implanted at any desired location within the CNS. For example, and without limitation, the polymer-based drug delivery device can be implanted either in the brain (*e.g.*, close to a site of damage such as an ischemic region following stroke, or in the opposite brain hemisphere), or in the base of the brain, in or near a CSF-filled space such as ventricle, *etc.* In the case of a device implanted into a CSF-filled space, the device releases the agent into the CSF, allowing it to diffuse to a region of the brain surround the space. Depending on the size of the device, it can also be implanted at or adjacent to a nerve, nerve tract, ganglion, *etc.*, of the PNS. For example, microimplants can be implanted within or internal to the epineurium or perineurium of a nerve.

Implantable Microchip-Based Delivery

[00197] In certain embodiments of the invention, one or more agent(s) is delivered to the nervous system using an external or implantable silicon or polymeric microchip, which contains from dozens to up to hundreds or thousands of microreservoirs, each of which can be filled with any combination of drugs, reagents, or other chemicals. Micro-reservoirs can be opened at predetermined times and/or on demand using preprogrammed microprocessors, remote control, or biosensors. If desired, complex chemical release patterns can be achieved using these approaches. In some embodiments, micro-reservoirs have "caps" that degrade over time. Release can be controlled by varying the thickness and/or composition of the cap, thereby allowing release to occur at predictable and substantially predetermined times. The cap material can be, *e.g.*, a degradable polymer. In some embodiments, the cap material is non-degradable and is permeable to the molecules to be delivered. The physical properties of the material used, its degree of crosslinking, and its thickness will determine the time necessary for the molecules to diffuse through the cap material. If diffusion out of the release system is limiting, the cap material delays release. If diffusion through the cap material is limiting, the cap material determines the release rate of the molecules in addition to delaying release time.

[00198] In some embodiments, the agent(s) to be delivered are inserted into the reservoirs in their pure form, as a liquid solution or gel, or they may be encapsulated within or by a release material. The release material may be, for example, a biodegradable or non-biodegradable polymer. Representative polymers include those mentioned above (see, *e.g.*, Santini *et al.*, 2000; U.S. Patents 5,797,898 and 6,808,522; and U.S. Patent Publications

2002/0072784, 2004/0166140, and 2005/0149000; for discussion of microchip-based delivery systems). Microchips can be implanted at any desired location in the CNS (as described above). Depending on the size of the device, it can also be implanted at or adjacent to a nerve, nerve tract, ganglion, *etc.*, of the PNS. For example, microchips can be implanted within or internal to the epineurium or perineurium of a nerve.

Methods for Focal Delivery

[00199] In certain embodiments of the invention, compositions comprising a plasticity-modifying agent and optionally a proteolysis enhancing agent are administered to a subject by focal delivery. Focal delivery may be accomplished in a number of different ways. Implantation of a polymer-based drug delivery device or microchip such as those described above at a site within the central nervous system or within or adjacent to a nerve, nerve tract, or ganglion within the peripheral nervous system is a suitable method to achieve focal delivery.

[00200] Internal (implantable) or external pumps can be employed for administering a substantially fluid composition of the invention. Such pumps typically include a drug reservoir from which continuous or intermittent release occurs into the target tissue or in the vicinity thereof via a catheter. In certain embodiments of the invention, treatment is carried out using an implantable pump and a catheter having a proximal end coupled to the pump and having a discharge portion for infusing therapeutic dosages of one or more agents described herein into a predetermined infusion site in brain tissue or into the spinal canal (intrathecal delivery).

[00201] Infusion (which term is used to refer to administration of a substantially fluid material to a location in the body by means other than injection) may be carried out in a continuous or nearly continuous manner, or may be intermittent. The pump may be programmed to release predetermined amounts of the agent at predetemined time intervals. U.S. Patent 4,692,147 (assigned to Medtronic, Inc., Minneapolis, MN) describes a suitable pump. In certain embodiments one or more of the infusion systems known as the Synchromed® Infusion System (manufactured by Medtronic, Inc., Minneapolis, MN; see web site having URL www.medtronic.com) is used. However, it will be appreciated that the pump may take the form of any device used for moving fluid from a reservoir. Mechanical, pressure-based, osmotic, or electrokinetic means may be used.

[00202] In order to deliver an agent to the brain parenchyma, a catheter attached to the pump may be implanted so that the discharge portion lies in the brain parenchyma (see, *e.g.*, U.S. Patent 6,263,237 for description of a variety of suitable systems and methods for implanting them into the body of a subject and directing the administration of an active agent to a desired location in the brain). Continuous ICM is a relatively new technique of regional delivery of therapeutic agents directly into brain parenchyma, which establishes a bulk flow current that has the potential to homogeneously distribute even large molecules (see, *e.g.*, Laske, 1997 for an example of administration of an agent to a region within the brain).

[00203] In certain embodiments of the invention, the agent is delivered to one or more of the CSF-containing cavities or chambers of the central nervous system, *e.g.*, the ventricles or cisterna magna, which is located at the bottom of the skull. As is well known in the art, there are two lateral ventricles and midline third and fourth ventricles within the brain. To deliver an agent to a ventricle or the cisterna magna using an infusion pump, the catheter may be implanted so that the discharge portion lies in the ventricle or the cisterna. The agent diffuses out of the ventricle or cisterna magna. Delivery to these locations therefore allows delivery of the agent to a relatively wide area of the brain rather than localizing it more closely to a specific site. Intraventricular or intracisternal administration is considered to be administration to the nervous system. In certain embodiments of the invention delivery to a CSF-containing space, *e.g.*, a ventricle, is accomplished by surgically implanting a catheter through the skull so that the tip has access to the space. The other end of the catheter is then connected to a reservoir (*e.g.*, an Ommaya reservoir), which is placed beneath the scalp (*i.e.*, subcutaneously). This method is in use for delivery of chemotherapeutic agents (see, *e.g.*, Ommaya and Punjab, 1963; Galicich and Guido, 1974; Machado, 1985; Obbens, 1985; and Al-Anazi, 2000).

[00204] If the subject suffers from damage to the spinal cord, the catheter is implanted so that the discharge portion lies in an intrathecal space of the spinal cord while the other end is connected to the pump reservoir. Methods for administering agents to the spinal fluid (*i.e.*, intrathecally) are well known in the art. Such methods are commonly used in the treatment of chronic pain, and are routinely used to deliver analgesic agents over a period of months. Similar methods are of use in the present invention (see, *e.g.*, Lamer, 1994; Paice, 1996; Winkemuller, 1996; Tutak, 1996; and Roberts, 2001 for descriptions of the use of implantable pumps for delivery of a variety of different therapeutic agents for treatment of a number of different conditions).

[00205] For delivery to the PNS, suitable methods include injection or infiltration into a nerve or nerve trunk, *e.g.*, adjacent to a site of nerve damage, and implantation of a polymer-based delivery device or microchip either adjacent to a site of nerve damage. Methods for administering anesthetic agents to diverse nerves, nerve bundles, *etc.*, within the PNS are well known in the art, and any of these methods are applicable in the context of the present invention.

[00206] In certain embodiments of the invention, a solution comprising a polymer, a plasticity-modifying agent, and optionally one or more additional active agents is administered by injection or infusion using any of the means described above. The polymer assembles to form a gel upon administration, *e.g.*, following contact with physiological fluids. Such assembly may, for example, be triggered by exposure to monovalent or divalent cations. For example, U.S. Publication 2002/0160471 describes self-assembling peptides that form hydrogels. U.S. Patent 6,129,761 describes a variety of different self-assembling polymers and polymers that require a polymerizing agent or cross-linking agent to faciliatate assembly. Certain of these polymers assemble to form hydrogel stuctures upon contact with physiological fluids following administration to a subject. In another embodiment a collagen-based system is used (see, *e.g.*, PCT Publication WO 00/47130, which describes injectable collagen-based systems for delivery of cells or therapeutic agents).

Delivery Location, Timing, Duration of Treatment, and Dose

[00207] The plasticity-modifying agent(s) can be administered using any route of administration, *e.g.*, oral, intravenous, intraperitoneal, intramuscular, intradermal, transdermal, subcutaneous, pulmonary (*e.g.*, by inhalation into the lungs), nasal, *etc.* The route and dose will be selected so as to achieve effective concentrations in the nervous system without undue side effects.

[00208] The location at which a composition of the invention is to be administered or implanted may be selected with relation to the particular condition being treated. For example, if the subject has suffered an injury or damage to the brain, *e.g.*, as a result of stroke, trauma, *etc.*, the composition may be delivered to the brain parenchyma or to one or more of the ventricles of the brain or to the cisterna magna. If the subject has suffered an injury or damage to the spinal cord, a composition of the invention may be delivered to the spinal cord, *e.g.*, by implanting or administering a composition within the spinal canal. If the plasticity-modifying agent or an inventive composition crosses the blood-brain barrier, it can

be delivered systemically, *e.g.*, by oral, intravenous, intraperitoneal, intramuscular, intradermal, transdermal, subcutaneous, pulmonary (e.g., by inhalation into the lungs), nasal, *etc.* administration.

[00209] The area to which the agent is to be administered may be, for example, an area that has been damaged (*e.g.*, an ischemic lesion) or an area adjacent to an area that has been damaged. The agent(s) may be administered to any region, nucleus, or functional area within the brain including, but not limited to, any of the major subdivisions of the brain (cortex, hippocampus, cerebellum, thalamus, midbrain, brain stem), which include motor cortex, sensory cortex including visual cortex, auditory cortex, and somatosensory cortex, language areas of cortex, frontal cortex, internal capsule, basal ganglia, thalamus, and/or other area noted above, *etc.* As noted above, numerous specific areas within the brain have been defined based on anatomical and histological considerations. In addition, areas in the brain that are responsible for performing various tasks have been defined on functional grounds and are well known in the art (see, *e.g.*, Kandel, *supra*; and Victor and Ropper, *supra*).

[00210] In certain embodiments of the invention, the area that has been damaged is identified. The area that has been damaged can be identified using a variety of different imaging techniques known in the art. For example, and without limitation, suitable methods include imaging techniques such as magnetic resonance imaging (MRI), optionally imaging features associated with blood flow such as perfusion, diffusion, or both, computed tomography (CT), positron emission tomography (PET), ultrasound, *etc.* Imaging techniques that image structure and/or function are available. Functional studies can be performed, *e.g.*, using labeled substrates such as glucose to identify regions of the brain that are metabolically inactive and/or that do not respond to stimulation, suggesting that they are functionally inactive (see, *e.g.*, Grossman and Yousem, *supra*).

[00211] Clinical diagnosis can be used instead of, or in addition to, imaging techniques. For example, the area to which damage has occurred can be identified by performing a neurological examination. Deficits noted on the neurological examination can be correlated with damage to particular areas of the central and/or peripheral nervous system (Kandel, *supra*; and Victor and Ropper, *supra*). In certain conditions, such as neuropsychiatric disorders of developmental or adult origin, a genetic test may be used in addition to a clinical diagnosis.

[00212] Any of the foregoing methods can be utilized acutely (*e.g.*, within hours to a few days of a damaging event such as stroke or injury) or at later times (*e.g.*, several days to weeks, months, or years following the event). The characteristic evolution of the appearance

of nervous system lesions is well known in the art, so the practitioner can readily identify the location of damaged tissue at any desired time point relative to the time at which the event causing the damage occurred.

[00213] In certain embodiments of the invention, the agent is delivered at or adjacent to a site where tissue necrosis and/or scar tissue formation has occurred in the CNS. Areas of necrosis can be identified using various imaging techniques such as those mentioned above. Symptoms may also be used to guide selection of an appropriate location at which to implant the matrix. For example, if a subject experiences impairment of a particular function such as movement, sensation, speech, *etc.*, then the portion of the brain that is normally responsible for control or achievement of that function, or the corresponding area on the contralateral side of the subject's body, may be selected as a suitable site for implantation of a drug delivery device of the invention. Standard surgical techniques can be used.

[00214] In some embodiments of the invention the agent is administered to an area adjacent to a region that has been damaged by an infarct, *e.g.*, to the peri-infarct area. Without wishing to be bound by any theory, peri-infarct regions are likely to be sites of clinically relevant cortical remodeling following stroke. For example, the agent may be administered to a site that is located up to approximately 0.5 cm from the edge of an infarcted area, up to 1.0 cm from the edge of an infarcted area, or up to 2 cm from the edge of an infarcted area. In some embodiments the agent is administered to a site immediately adjacent to an infarcted area, *e.g.*, up to 0.5 cm from the edge of the infarcted area. In some embodiments of the invention the agent is administered to the ischemic penumbra adjacent to an area of severe ischemia following stroke (see, *e.g.*, Furlan *et al.*, 1996). The ischemic penumbra is a region of brain tissue that experiences mild to moderate ischemia but remains viable for a period of time following a stroke (*e.g.*, up to several hours or longer) and may be salvageable if perfusion is re-established and/or through the use of neuroprotective agents. The ischemic penumbra may be operationally defined using, *e.g.*, diffusion and perfusion MRI (Schlaug *et al.*, 1999; and Kidwell *et al.* 2003). One of ordinary skill in the art will be able to select an appropriate definition and measurement technique.

[00215] In some embodiments of the invention, the agent is administered to a location on the opposite side of the brain from the side where damage has occurred. The site of administration may be substantially symetrically located with respect to the region that has been damaged. Without wishing to be bound by any theory, it is possible that following damage to a particular region of the brain, the contralaterally located region reorganizes so as to assume responsibility for functions that were previously performed by the damaged region.

For example, a portion of the brain that normally (*e.g.* prior to injury) generates movement commands for the left hand only may reorganize so as to generate commands to both hands following damage to a portion of the brain that previously commanded the right hand.

[00216] As mentioned above, delivery by injection or infusion pump is suitable for compositions in which an agent of the invention is dissolved in a liquid and for compositions comprising microparticles of suitable dimensions. The polymer-based drug delivery devices of the invention will typically be implanted into the subject in an appropriate location in the nervous system so that they will release the active agent at a desired location. For example, they may be implanted into the brain parenchyma. They may also be implanted into a ventricle or into the spinal canal in various embodiments of the invention. The location for implantation is selected so as to achieve an effective concentration of the active agent at a desired location in the nervous system, *i.e.*, typically reasonably close to the location at which it is desired to achieve the effective concentration. Care is taken to avoid disrupting undamaged portions of the nervous system to the extent possible. Imaging may be used to guide administration or implantation of the compositions and drug delivery devices of the invention, *e.g.*, they may be administered or implanted under stereotactic guidance.

[00217] The agent(s) can be administered in a continuous or intermittent fashion. Intermittent or pulsatile delivery may be performed at times selected in accordance with the active half-life of the agent in order to maintain a therapeutically useful dose and/or may be performed in accordance with physiological patterns such as circadian rhythms, or during periods when the subject either is or is not engaged in particular activities. If the agent is administered using an implanted device such as a pump or microchip, an external controller may be used to trigger release at a desired time, or the device can be programmed to release the agent at particular times or intervals.

[00218] In some embodiments, compositions of the invention may be administered to a subject following an event that damages the brain or spinal cord or following diagnosis of a neuropsychiatric or neurodevelopmental disorder for a finite period of time. For example, compositions of the invention may be administered to a subject for up to 1 week, up to 4 weeks, up to 2 months, up to 6 months, up to 12 months, up to 18 months, up to 2 years, up to 5 years, up to 10 years, up to 20 years, or even longer. In some embodiments, compositions of the invention may be administered to a subject following an event that damages the brain or spinal cord or following diagnosis of a neuropsychiatric or neurodevelopmental disorder for the rest of the subject's life.

[00219] In some embodiments, compositions of the invention are not administered immediately after an event that damages the brain or spinal cord or following diagnosis of a neuropsychiatric or neurodevelopmental disorder. To give but a few examples, administration may be initiated after certain other therapeutic strategies (*e.g.* behavioral therapies) have been performed; after the subject has reached a desired level of health; after the subject has reached a desired age; *etc.*. In some embodiments, compositions of the invention are administered at least 1 week, at least 4 weeks, at least 2 months, at least 6 months, at least 12 months, at least 18 months, at least 2 years, at least 5 years, at least 10 years, at least 20 years, or even longer, after an event that damages the brain or spinal cord or following diagnosis of a neuropsychiatric or neurodevelopmental disorder.

[00220] In some embodiments, compositions of the invention may be administered for a period of time and may then be discontinued. For example, administration may be discontinued when the subject responds to the administration (*e.g.* if symptoms improve, if damage is reversed, if plasticity has been modified, if function has been restored to the nervous system, if neural development has been stimulated, *etc.*). To give another example, administration may be discontinued when the subject has reached at least one desired endpoint or treatment milestone. In some embodiments, compositions of the invention may be administered to a subject for up to 1 week, up to 4 weeks, up to 2 months, up to 6 months, up to 12 months, up to 18 months, up to 2 years, up to 5 years, up to 10 years, up to 20 years, or even longer, before being discontinued. In some embodiments, administration of compositions of the invention that has been discontinued may be resumed at any point in time after discontinuing the administration. To give but one hypothetical example, (i) a plasticity-modifying agent may be administered to a subject following diagnosis with a neurodevelopmental disorder; (ii) the subject's symptoms may disappear; (iii) administration of the plasticity-modifying agent may be discontinued; (iv) the symptoms may return; and (v) administration of the plasticity-modifying agent may be resumed. In some embodiments, administration may be discontinued for up to 4 weeks, up to 2 months, up to 6 months, up to 12 months, up to 18 months, up to 2 years, up to 5 years, up to 10 years, up to 20 years, or even longer, before administration is resumed.

[00221] In certain embodiments of the invention, the compositions of the invention are administered at times varying from immediately after to considerably after, *e.g.*, least 3 hours after, the onset or occurrence of a damaging event such as a stroke or injury. For example, the initial administration may be a few minutes to hours, *e.g.*, at least 6, 12, 24, 36, or 48 hours after the onset or occurrence of a damaging event. In certain embodiments of the

invention the initial administration is between 24 hours and 1 week after the onset or occurrence of a damaging event, between 1 week and 1 month after the onset or occurrence of a damaging event, or between 1 and 3 months, 3 and 6 months, 6 and 12 months after the onset or occurrence of a damaging event, *etc.* The initial administration may occur at times greater than 1 year following the onset or occurrence of a specific damaging event, *e.g.*, between 1-5 years, *etc.* In some embodiments of the invention the initial administration occurs after the subject has reached a plateau of functional recovery. For example, the subject may have failed to display improvement on one or more standardized tests, or may have failed to experience subjective improvement during the preceding 1-3 months, 3-6 months, or longer. For treatment of neuropsychiatric disorders, neurodegenerative diseases, nutrient deprivation, neoplastic diseases, and other conditions for which there is no specific identifiable damaging event, administration can occur at any time following diagnosis of the disease.

[00222] The total time period during which treatment occurs, and the number of treatments within such time period, can vary. The total duration of treatment (*i.e.*, the time interval between the first and the last treatment) can range from days to weeks, months, or years. For example, the total duration may be 1 day; 1 week; 4 weeks; 1, 3, 6, 9, or 12 months, between 1 and 2 years; 2 and 5 years; 2 and 10 years; 2 and 20 years; *etc.* If the agent is administered in discrete doses in addition to or instead of being administered continuously, subjects may receive anywhere from a single dose to dozens or even hundreds or thousands of doses. The time interval between doses can be varied. It may, for example, be desirable to administer the agent for a defined time period each day, *e.g.*, 10 minutes/day, 1 hr/day, *etc.*

[00223] The dose of the plasticity-modifying agent will be selected taking into account the particular agent, the condition being treated, the route of administration, and other relevant factors. The dose (or doses) may be, *e.g.*, an amount effective to promote growth or sprouting of axons, promote structural reorganization of synaptic connections, increase formation of new synaptic connections, increase dendritic spine motility, inhibit structural or functional degeneration (*e.g.*, degeneration that would otherwise be expected to take place) or any combination of the foregoing. The dose may range from about 0.001 to 100 mg/kg body weight, *e.g.* from about 0.01 to 25 mg/kg body weight. The dose may, for example, range between 1 μg/kg and 100 mg/kg, *e.g.*, between 10 μg/kg and 10 mg/kg. Exemplary doses range from 0.1 to 20 mg/kg body weight, *e.g.*, about 1 to 10 mg/kg.

[00224] The dose of the proteolysis-enhancing agent will be selected to enhance the effect of the plasticity-modifying agent. Typically the dose for each administration of the proteolysis-enhancing agent will be significantly lower than the dose that would be required to cause lysis of a significant blood clot when administered to the vascular system. Exemplary, non-limiting doses ranges for a proteolysis-enhancing agent, *e.g.*, tPA, include one or more of the following: (i) a dose sufficient to achieve a concentration of between 10 and 100,000 IU/ml or between 100 and 10,000 IU/ml or between 100 and 1,000 IU/ml in the extracellular fluid or in a CSF-containing cavity such as a ventricle or the spinal canal; a dose between 1 μg/day and 10 mg/day; a dose between 1 μg/day and 1 mg/day; a dose 5 μg/day and 500 μg/day; a dose between 10 μg/day and 100 μg/day, *etc.*

[00225] Various dosing regimens may be used. For example, it may be desirable to give a relatively large "loading dose" initially and then administer smaller doses either continuously or intermittently so as to maintain an effective concentration in the region of the nervous system being treated. It will also be appreciated that, in general, the more focally directed the delivery, the lesser the total dose that may be required. Thus direct administration via a catheter to a specific brain region may require a lower total dose than delivery to a ventricle. Furthemore, the larger the area of damage and/or the greater the amount of reorganization and/or recovery required, the larger might be the dose. .

[00226] If desired, the concentration of the plasticity-modifying agent (or any other agent whose administration is contemplated in the present invention) can be monitored, *e.g.*,. in the CSF of the subject. The dose can be adjusted accordingly to obtain a desired concentration.

[00227] In certain embodiments of the invention the agent(s) is/are administered, *e.g.*, released, in a defined temporal relation to rehabilitative therapy, *e.g.*, during, prior to, or following engagement of the subject in one or more rehabilitative activities. The agent(s) may, for example, be administered up to 5 minutes to 12 hours prior to the activity, up to 5 minutes to 12 hours after the activity, during the activity, or immediately prior to or immediately following the start of a therapy session, *e.g.*, up to 5 minutes prior to the beginning of a therapy session or up to 5 minutes following the start of a therapy session. By "therapy session" is meant any period of time in which the subject is engaged in performing activities that have been suggested or prescribed by a health care provider for purposes of assisting the functional recovery of the subject following damage to the CNS or PNS or for improving the functioning of a subject suffering from a neurodevelopmental disorder. The health care provider need not be present during the therapy session, *e.g.*, the subject may

perform the activities independently or with the assistance of personnel other than a health care provider.

Administration of Additional Active Agent(s), Cells, and Gene Therapy

[00228] In various embodiments of the invention, one or more additional active agents is administered to the subject in conjunction with administration of the plasticity-modifying agent and, optionally, the proteolysis-enhancing agent. The additional active agents may be administered concurrently or sequentially. The additional active agent may be delivered focally but may alternatively be administered systemically using any suitable route of administration (*e.g.*, oral, intravenous, intramuscular, subcutaneous, transdermal, pulmonary, nasal, *etc.*). The additional active agent may be delivered in the same solution or dosage form as the proteolysis-enhancing agent. The additional active agent may be incorporated into a polymeric matrix together with the proteolysis-enhancing agent and delivered via a polymer-based drug delivery device or delivered using a pump or any other delivery system disclosed herein.

[00229] In some embodiments of the invention an agent other than a proteolytic agent is administered, wherein the agent cleaves one or more components of the extracellular matrix at a bond other than a peptide bond. For example, the agent may cleave a polysaccharide portion of an ECM component such as a proteoglycan or glycosaminoglycan. Examples of suitable agents include chondroitinases (which cleave chondroitin sulfate and hyaluronic acid), hyaluronidases, heparinases (which cleave heparin), heparanase (which cleaves heparan sulfate), *etc.*

[00230] In certain embodiments of the invention, the additional active agent is a neural growth enhancing agent. A neural growth enhancing agent is any molecule or cell that promotes, enhances, increases, *etc.*, one or more aspects of the growth or regeneration of neural tissue. For example, the molecule or cell may promote axon growth. A neural growth enhancing agent, as used herein, can be a neurally active growth factor, neurotransmitter or neurotransmitter analog, neurally active metal, modulator of a synaptic signaling molecule, or cell. It will be understood that typically "cell," as used in this context, refers to multiple cells. The term "neurally active" means that the agent exerts a biological effect on neural tissue. For example, the agent may exert an effect that enhances structural and/or functional nervous system reorganization or recovery.

[00231] The invention therefore provides compositions comprising a plasticity-modifying agent, a neural growth enhancing agent, and, optionally a proteolysis-enhancing agent. The invention provides drug delivery devices comprising the composition. The drug delivery device can be, for example, any of the drug delivery devices described herein.

[00232] The invention further provides methods for promoting recovery or reorganization in the nervous system of a subject comprising the step of: administering a plasticity-modifying agent, a neural growth enhancing agent, and, optionally a proteolysis-enhancing agent to a subject in need of enhancement of recovery or reorganization of the nervous system. The subject is typically in need of recovery or reorganization of the nervous system as a result of ischemic, hemorrhagic, neoplastic, degenerative, traumatic, and/or neurodevelopmental damage to the nervous system. The invention provides methods of treating a subject in need of enhancement of recovery or reorganization in the nervous system comprising the step of: administering a plasticity-modifying agent, a neural growth enhancing agent, and, optionally a proteolysis-enhancing agent to the subject. The subject is typically in need of enhancement of recovery or reorganization of the nervous system as a result of ischemic, hemorrhagic, neoplastic, degenerative, traumatic, and/or neurodevelopmental damage to the nervous system. Any of the agents in the aforementioned methods can be administered focally to the central or peripheral nervous system either individually or in combination using any of the methods described herein. Either or both of the agents can be administered by any alternate route of administration. Certain features of this aspect of the invention, *e.g.*, dose ranges, adjunct therapy, *etc.*, can be similar to those described for other aspects of the invention.

[00233] Neurally active growth factors include, but are not limited to, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-1 (NT-3), neurotrophin-4/5 (NT-4/5), ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), glial cell derived growth factor (GDNF), neurturin, artemin, persephin, acidic or basic fibroblast growth factor (aFGF, bFGF), osteogenic protein-1 (OP-1), vascular endothelial growth factor (VEGF), erythropoietin (EPO), and granulocyte colony stimulating factor (G-CSF).

[00234] "Synaptic signaling molecules" refer to endogenous molecules that are activated downstream of calcium entry into cells through synaptic activation or following release of calcium from intracellular stores and that transduce electrical activity into structural changes in neurons. These include a variety of kinases such as calcium/calmodulin-dependent protein kinase II and IV, protein kinase C (PKC), protein kinase A (PKA), extracellular signal regulated kinase (ERK), cyclic AMP (cAMP) dependent kinase, along with molecules such

as cyclic AMP response element binding protein (CREB), activity regulated cytoskeletal associated protein (arc), troponin C; and Rac and Rho pathways and their associated kinases. G protein coupled receptors transduce information from the extracellular space to intracellular signals (among other activities) and are also considered to be synaptic signaling molecules. Modulators (*i.e.*, agents that activate or inhibit) of a number of these signaling molecules are known in the art and are of use in the present invention. Molecules that can bind to G protein coupled receptors importantly include those that can activate or inhibit (a) PKA and cAMP; (b) cyclic GMP, and (c) PKC. Pathways downstream of GPCR activation importantly regulate CREB, BDNF, actin, reorganization of the dendritic and axonal cytoskeleton, *etc.* By way of example, activators of cAMP include Sp-cAMPS (Sigma), which may to be delivered into the brain at a typical dose of 0.02-0.5 μg/kg/day, and Rolipram® (Sigma), which can be given intramuscularly at a dose of 1-100 μg/kg/day (Ramos *et al.*, Neuron 2003). Rolipram is a phosphodiesterase inhibitor, which prevents breakdown of cAMP. Inhibition of cAMP can also, under certain conditions, have a stimulatory effect on synapses and is of use in certain embodiments of the invention. Inhibitors of cAMP include Rp-cAMPS (Sigma), which can be delivered into the brain at a typical dose of 0.02-0.5 μg/kg/day (Ramos *et al.*, 2003).

[00235] An activator of cGMP is 8-Br-cGMP; an inhibitor is Rp-cGMPs. Both are typically delivered focally. Effective doses on neurite growth and dynamics in brain slices are about 10-100 μM (Nishiyama *et al.*, 2003). Another inhibitor is ODQ; an effective dose for influencing axon growth is about 10 μM (Leamey *et al.*, 2001). Activators of PKC include diacylglycerol and phosphatidylserine. An inhibitor is a drug called GF109203X (GFX). Effective doses in slices are approximately10-100 μM (Nishiyama *et al.*, 2003).

[00236] It is noted that doses presented here should in no way be considered limiting. In general, the invention encompasses doses at least 10 to 100 fold lower than those described here, and doses up to the maximum tolerated dose of the agent, as consistent with sound medical judgment. Furthermore, dosage routes for specific agents are mentioned here by way of example and are not intended to be limiting. In general, any suitable route of administration can be used. In particular, any of these agents may be administered using the methods for focal administration described herein.

[00237] Neurally active small molecules include a number of the modulators and neurotransmitters described above as well as diverse compounds known in the art to influence nervous system function (see, *e.g.*, *Goodman and Gilman, supra*; and Kandel, *supra*).

[00238] Neurotransmitters are naturally occurring compounds that generally fall into the categories of small molecules (*e.g.*, catecholamines) and peptides. A neurotransmitter for use in the present invention can be excitatory or inhibitory. Exemplary neurotransmitters include, but are not limited to, acetylcholine, dopamine, serotonin, glycine, glutamate, epinephrine, norepinephrine, and gamma aminobutyric acid (GABA). A neurotransmitter analog as used herein is a compound other than a naturally occurring neurotransmitter that exerts an excitatory or inhibitory effect on a neurotransmiter receptor. The analog will typically bear a structural resemblance to a naturally occurring neurotransmitter and will compete with it for binding to its receptor.

[00239] Neurally active metals include magnesium and zinc. The magnesium and/or zinc can be provided in any suitable form. Typically the metal will be provided in the form of a salt that contains a metal cation and an anion that serves as a counterion. The counterion can be an organic or inorganic substance. For example, the counterion can be phosphate, carbonate, gluconate, citrate, sulfate, acetate, maltonate, oxalate, or any other pharmaceutically acceptable ion such as those mentioned below. In some embodiments the metal cation is provided as a chelate, in which the metal cation is complexed with an organic molecule such as a heterocyclic ring.

[00240] Gene therapy methods may be used to increase expression of genes that encode products, *e.g.*, plasticity-enhancing agents, proteolysis-enhancing agents, and/or agents that promote nervous system functional and/or structural reorganization and/or recovery. Gene therapy encompasses delivery of nucleic acids comprising templates for synthesis of a molecule of interest to a cell of interest. The nucleic acid (or a nucleic acid derived from the nucleic acid as, for example, by reverse transcription) may be incorporated into the genome of the cell or remain permanently in the cell as an episome. Gene therapy also encompasses delivery of nucleic acids that do not integrate or remain permanently in the cell to which they are delivered. Such approaches permit temporary or transient synthesis of a molecule of interest. Methods and materials for performing gene therapy are well known in the art and will not be extensively reviewed here (see, *e.g.*, Berry, 2001; Han, 2000; and Thomas and Klibanov, 2003).

[00241] Vectors and delivery vehicles (*e.g.*, polymeric matrices) that provide nucleic acids comprising templates for synthesis of polypeptides may be incorporated into a composition of the invention or administered separately. Typically, the nucleic acid includes a coding sequence for a gene to be expressed in a cell of interest and also includes appropriate expression signals, *e.g.*, promoters, terminators, *etc.*, to ensure proper expression.

[00242] In general, either viral or non-viral vectors may be used. For example, herpes virus, adenovirus, adeno-associated virus, retroviruses, or lentiviruses may be used. It may be desirable to avoid the use of intact viruses in delivering templates to cells. Thus it may be desirable to deliver DNA vectors or linear DNA molecules. These vectors may, but need not, include viral sequences such as long terminal repeats, *etc.* Any of a wide variety of agents useful for transfection may be used to enhance uptake of nucleic acids by cells. Vectors are taken up by cells in the nervous system, and the polypeptide of interest is expressed and, usually secreted.

[00243] In some embodiments of the invention, cells are administered to a subject. In some embodiments of the invention, cells serve as a source for a plasticity-enhancing agent. For example, the cells may secrete IGF1 into the extracellular space. In certain embodiments of the invention, cells are genetically modified prior to their administration to increase their synthesis of a plasticity-enhancing agent. For example, cells may be stably transformed with a vector that comprises a template for transcription of an RNA that encodes the agent. Cells may be sequestered in a non-biodegradable reservoir or compartment that retains them at a particular location and prevents their integration with cells at the site of administration or their wider dispersal.

[00244] In some embodiments of the invention, cells are administered to a subject who may receive a composition comprising a plasticity-modifying agent and optionally a proteolysis-enhancing agent. In some embodiments cells contribute to structural and/or functional recovery of the nervous system. Cells can be neurons, glia, or non-neural cells. Suitable cells include, but are not limited to, Schwann cells and olfactory ensheathing glia (Bunge, 2003). Cells can be of a single cell type, or combinations of different cell types can be administered. Cells may replace or supplement neural tissue that has been irreversibly damaged and/or provide supportive functions. In some embodiments, neural stem cells are administered. Multipotent neural stem cells, capable of giving rise to both neurons and glia, line the cerebral ventricles of all adult animals, including humans. Distinct populations of nominally glial progenitor cells, which also have the capacity to generate several cell types, are dispersed throughout the subcortical white matter and cortex (Goldman 2005). In some embodiments, adult or embryonic stem cells are administered. Such cells can be derived from a location outside the nervous system, *e.g.*, the bone marrow, liver, umbilical cord, *etc.* Cells of any type can be used. Cells can be autologous or non-autologous. In certain embodiments, cells are from the same species as the subject.

[00245] In certain embodiments of the invention the cells are administered in a polymeric scaffold, made of certain of the materials such as those described above that provide a hospitable environment to maintain cell viability. The polymer material may be biodegradable. The matrix or scaffold may be formed prior to implantation into the nervous system of a subject or may form following administration, *e.g.*, upon contact with physiological fluids. Encapsulation of cells in a variety of different polymeric matrices or scaffolds is well known in the art (see, *e.g.*, U.S. Patents 6,129,761 and 6,858,229; U.S. Patent Publication 2002/0160471; and Teng, 2002).

[00246] In addition to or instead of the various active agents described above, which are selected primarily based on their useful properties for enhancing structural or functional recovery or reorganization in the nervous system, various other substances can be administered. Such substances include, but are not limited to, antibiotics or antifungal agents to treat or reduce the risk of infection, chemotherapeutic agents to treat tumors, *etc.*

[00247] It is to be understood that the invention explicitly includes compositions comprising each specific combination of any of the proteolysis-enhancing agents described herein, optionally in combination with any of the proteolysis-enhancing agents described herein and/or any of the the additional active agents described herein. Because it would not be practical to list each and every combination, only a few examples are provided here. For example, the invention includes a composition comprising IFNγ and tPA. The composition may further include a neurally active growth factor (*e.g.*, BDNF). The invention also includes a composition comprising tPA and a modulator of a synaptic signaling molecule (*e.g.*, tPA and Rolipram); a composition comprising tPA and a neurotransmitter (*e.g.*, tPA and serotonin); a composition comprising tPA and a neurally active metal (*e.g.*, tPA and magnesium); a composition comprising tPA and a neurally active small molecule; a composition comprising tPA and a cell (*e.g.*, tPA and a neural stem cell), *etc.* Similarly, the invention includes compositions comprising (i) plasmin and (ii) a neurally active growth factor, a synaptic signaling molecule, a neurotransmitter, a neurally active metal, and/or a cell. Compositions comprising 3, 4, 5, or more of the proteolysis-enhancing agents and/or additional agents are encompassed. The invention provides a polymer-based drug delivery device comprising any of these compositions and an implantable microchip comprising any of these compositions or designed to administer the agents individually.

[00248] The invention encompasses administration of one or more of any of the proteolysis-enhancing agents described herein in conjuction with one or more of any of the

additional agents described herein to a subject in need of reorganization and/or recovery of the nervous system. The subject has typically experienced ischemic, hemorrhagic, neoplastic, traumatic, degenerative, and/or neurodevelopmental damage to the central or peripheral nervous system. Agents can be administered together or separately. In some embodiments both the proteolysis-enhancing agent(s) and the additional agent(s) are administered focally. In some embodiments, the proteolysis-enhancing agent(s) are administered focally to the nervous system and the additonal agent(s) are administered by an alternate route (*e.g.*, intravenously or orally).

Therapeutic Applications and Adjunct Therapy

[00249] The compositions and methods of the invention are of use in treating subjects who have experienced events such as stroke or injury (*e.g.*, due to accident or surgery). The compositions and methods of the invention find use for treating subjects suffering from a variety of other diseases and conditions including, but not limited to, neurodegenerative diseases such as multiple sclerosis, amyotrophic lateral sclerosis, subacute sclerosing panencephalitis, Parkinson's disease, Huntington's disease, muscular dystrophy, and conditions caused by nutrient deprivation or toxins (*e.g.*, neurotoxins, drugs of abuse). Certain of the compositions and methods are of use for treating neurodevelopmental diseases such as autism or dyslexia, *i.e.*, diseases in which at least a portion of the nervous system fails to develop normal structure and/or function. Certain of the compositions and methods are of use for treating neuropsychiatric diseases such as schizophrenia and bipolar disorders, *i.e.*, diseases in which at least a portion of the nervous sytem fails to achieve its typical level of cognitive function. Certain of the compositions and methods are of use for providing cognitive enhancement and/or for treating cognitive decline, *e.g.*, "benign senescent forgetfulness," "age-associated memory impairment," "age-associated cognitive decline," *etc.* (Petersen 2001; Burns 2002). These terms are intended to reflect the extremes associated with normal aging rather than a precursor to pathologic forms of memory impairment. Thus these conditions are distinct from Alzheimer's disease. Certain of the compositions and methods are of use for treating Alzheimer's disease. In certain embodiments of the invention, the subject does not have, *e.g.*, has not been diagnosed with, Alzheimer's disease. In certain embodiments of the invention the subject is not suspected of having Alzheimer's disease. In certain embodiments of the invention the subject has not been identified as having an increased risk for developing Alzheimer's disease. Methods for treating or preventing

Alzheimer's disease, to the extent that any such methods are described and/or enabled in PCT Publication WO 01/58476 are explicitly excluded from certain embodiments of the instant invention.

[00250] Any of a wide variety of functional impairments may be treated using the compositions and methods of the invention. In some embodiments, compositions are used to promote restoration of respiratory function after spinal cord injury (SCI). For this purpose, compositions are typically administered to the spinal cord, *e.g.*, intrathecally. If desired, administration can be localized to the region of the spinal cord injury, *e.g.*, the cervical region of the spinal cord. Respiratory disorders are the leading cause of morbidity and mortality after SCI, affecting nearly half of all patients with a neurological deficit after SCI. Respiratory impairments resulting from cervical SCI, the most common clinical case, frequently render survivors chronically or permanently ventilator dependent, a sequelae which can dramatically compromise quality of life. There are no drug treatments for breathing disorders associated with SCI. Studies have established that the breathing system posseses a highly dynamic system of neuroplasticity which manifests both at the developmental stage as well as at the adulthood. Work in the laboratory of one of the inventors has demonstrated that even with nearly 50% phrenic respiratory motor region loss in the adult rat spinal cord, respiratory function can recover spontaneously in 5-6 weeks after a mid-cervical spinal cord injury. While the ultimate outcome from this neuroplasticity-mediated event is encouraging, the required lengthy period imposes serious life or death challenges to SCI patients. The present invention may significantly stimulate post-SCI respiratory neural circuit reorganization, and thus may quickly restore respiratory function after incomplete spinal cord transection, which is a frequent clinical occurrence.

[00251] Surgery for various conditions can sometimes result in damage to nerves. In some embodiments of the invention, the compositions and methods are used to regenerate, repair or otherwise restore function after nerves of the PNS supplying muscles, organs, or other parts of the body, or carrying information from a part of the body, have been necessarily or accidentally disconnected or damaged during surgery. In some embodiments, the present invention is used to regenerate, repair or prevent degeneration of nerves, *e.g.*, nerves supplied by the spinal cord to the muscles, organs, or other parts of the body, or that enter the spinal cord from sensory receptors from the body. Some embodiments include regeneration or repair of damaged or degenerated nerves in the CNS, for example the optic nerve or the auditory nerve, or prevention of degeneration of axon tracts or fiber bundles in the CNS due to diseases, disorders, and/or damage. These embodiments include, but are not limited to, the

regrowth, recovery, repair or prevention of degeneration of ascending or descending fiber tracts and connections in the spinal cord, and of fiber tracts and connections in other structural and functional subdivisions of the CNS. Some embodiments include rewiring or reorganizing brain pathways so as to elicit novel functions from existing brain regions. An example of this embodiment is enhancement of brain function, particularly when coupled with practice regimens that engage specific brain regions.

[00252] In certain embodiments of the invention, the subject to whom a composition of the invention is administered is engaged in a program of rehabilitative therapy or training. Such programs typically ensue after injury or stroke, but also include programs of remediation and training in a variety of disorders of developmental or adult onset. Such programs are commonly employed in disorders such as dyslexia, autism, Asperger's Syndrome, Pervasive Developmental Disorders – Not Otherwise Specified, Tourette's Syndrome, Personality Disorders, Schizophrenia and related disorders (see, *e.g.*, Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., DSM-IV, American Psychiatric Association, 1994, *Diagnostic and Statistical Manual*, Am. Psychiatric Assoc., Washington, DC for discussion of these disorders). Numerous rehabilitation programs for victims of stroke, spinal cord injury, and/or other forms of nervous system damage are known to those skilled in the art, and the subject can be engaged in any such program (see, *e.g.*, Gillen and Burkhardt, *supra*, for a discussion of suitable programs for victims of stroke). Similar programs may be used for victims of other forms of damage to the brain (see, *e.g.*, Somers, *supra*, for a discussion of suitable programs for victims of spinal cord damage). Suitable programs for individuals suffering from damage to the PNS are also known in the art. A rehabilitation program is typically designed and recommended by a health care provider with knowledge in the area of rehabilitative therapy. Therapy sessions may involve the participation of a health care provider. However, the subject may also engage in sessions or tasks associated with the program without the assistance or supervision of the health care provider.

[00253] The subject can be engaged in the program in a defined temporal relation with respect to the administration of the agent. For example, the subject can be engaged in the program during a time period in which the agent is being administered and/or during which the agent is present in effective amounts in the nervous system. In some embodiments, a dose of the agent is administered within a defined time period prior to engagement of the subject in a particular rehabilitative session or task. For example, the agent may be administered and/or may be present in an effective amount at any time up to 24 hours, 48 hours, or up to 1 week prior to the time at which the subject will be engaged in the session or

task, or the agent may be administered and/or may be present in an effective amount at any time up to 24 hours, 48 hours, or up to 1 week following completion of the session or task. Typically the subject will be engaged in the program over a period of weeks, months, or years, *i.e.*, the subject will participate in multiple therapy sessions over a period of time. The subject's participation in such sessions can be coordinated with administration of the agent so as to achieve an optimal effect. The beneficial effects of rehabilitative therapy may at least in part be due to structural and/or functional reorganization that occurs as a result of such therapy. Without wishing to be bound by any theory, the inventors propose that the proteolysis-enhancing activities and/or synaptic plasticity activities of the agents disclosed herein may facilitate this process. Thus an at least additive and potentially synergistic effect may result.

[00254] The methods and compositions of the invention may be tested using any of a variety of animal models for injury to the nervous system. Models that may be used include, but are not limited to, rodent, rabbit, cat, dog, or primate models for thromboembolic stroke (Krueger and Busch, 2001; Gupta, 2004), models for spinal cord injury (Webb *et al.*, 2004), *etc.* (see Examples 6 and 7 and references in Schmidt and Leach, 2003). The methods and compositions may also be tested in humans.

[00255] A variety of different methods, including standardized tests and scoring systems, are available for assessing recovery of motor, sensory, behavioral, and/or cognitive function in animals and humans. Any suitable method can be used. To give but one example, the American Spinal Injury Association score, which has become the principal instrument for measuring the recovery of sensory function in humans, could be used (see, *e.g.*, Martinez-Arizala A., 2004; Thomas and Noga, 2004; Kesslak JP and Keirstead HS, 2003; for examples of various scoring systems and methods).

[00256] Desirable dose ranges for use in humans may be established by testing the agent(s) in tissue culture systems and in animal models taking into account the efficacy of the agent(s) and also any observed toxicity.

Pharmaceutical Compositions

[00257] Suitable preparations, *e.g.*, substantially pure preparations of the proteolysis-enhancing agents, optionally together with one or more additional active agents, may be combined with pharmaceutically acceptable carriers, diluents, solvents, *etc.*, to produce an appropriate pharmaceutical composition. In general, methods and ingredients for producing

pharmaceutical compositions known to one of skill in the art are used. The desription herein is for exemplary purposes and is not intended to be limiting. It is to be understood that the pharmaceutical compositions of the invention, when administered to a subject, are typially administered for a time and in an amount sufficient to treat the disease or condition for whose treatment they are administered. Suitable modes of administration and formulations are described herein.

[00258] Further provided are pharmaceutically acceptable compositions comprising a pharmaceutically acceptable derivative (*e.g.*, a prodrug) of any of the agents of the invention, by which is meant any non-toxic salt, ester, salt of an ester or other derivative of an agent of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, an agent of this invention or an active metabolite or residue thereof. As used herein, the term "active metabolite or residue thereof" means that a metabolite or residue thereof also possesses similar activity to the parent agent. For example, rather than administering an active polypeptide, a zymogen (*i.e.*, an inactive or less active enzyme pre-cursor that requires a biochemical change, such as a hydrolysis reaction revealing the active site, for it to become an active enzyme) could be administered.

[00259] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the agent with which it is formulated. Furthermore, it is recognized that preparation methods for the pharmaceutical compositions are typically selected so as to not substantially reduce the activity of the agent with which they are formulated.

[0001] Pharmaceutically acceptable salts of certain of the agents of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates. Salts derived from appropriate bases include alkali metal (*e.g.*, sodium and potassium), alkaline earth metal (*e.g.*, magnesium), ammonium and N+(C1-4

alkyl)4 salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

[00260] A pharmaceutical composition is formulated to be compatible with its intended route of administration. Pharmaceutical compositions suitable for injection or infusion typically include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. Suitable carriers include physiological saline, bacteriostatic water, water for injection, dextrose solutions, phosphate buffered saline (PBS), or Ringer's solution. Antibacterial and/or antifungal agents; chelating agents, such as ethylenediaminetetraacetic acid; buffer,s such as acetates, citrates, or phosphates; and agents for the adjustment of tonicity, such as sodium chloride or dextrose, can be included. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. It may be advantageous to formulate the compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active agent(s) calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The preparation can, for example, be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[00261] Sterile injectable or infusable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent, optionally with one or a combination of ingredients enumerated above, followed by filtered sterilization. Typically solutions are free of endotoxin. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and optionally other ingredients. In the case of sterile powders for the preparation of sterile solutions, the usual methods of preparation are vacuum drying and freeze-drying (*e.g.*, lyophilization) which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Examples

Example 1: Identification and Analysis of Genes that are Differentially Regulated Under Visual Deprivation Paradigms

Materials and Methods

RNA Preparation and Microarray Analysis

[00262] Studies were performed in mice (129/SvEv) at the peak of the critical period[28], postnatal day (P) 27. All animal protocols were approved by MIT's Committee on the Care and Use of Animals and followed NIH guidelines. For monocular deprivation (MD), animals were anesthetized with avertin (0.016 ml/g) and the eyelids of one eye sutured (at P11-12 for 15-16 days for microarray analyses). For dark-reared (DR) animals (aged P27-30), the procedure was the same described above, with the exception that the animals were anesthetized in darkness and not exposed to light until deeply anaesthetized; in these mice only the binocular response was evaluated and compared to that in control animals.

[00263] In a first set of experiments we extracted total RNA from V1 of normally reared P27 mice (control, n=3 samples), from V1 of P27 mice born and reared in darkness (DR, n=3 samples), and from V1 contralateral to the deprived eye of P27 mice in which monocular deprivation was started at P11-12, before eye-opening (MD, n=6 samples; three samples were done with deprivation of the right eye and 3 with deprivation of the left eye; these 6 samples were considered as a group because no significant differences were observed between right and left eye deprivation). For each sample, animals came from different litters and the tissue was derived from V1 of at least two different animals. In both groups of animals, monocular and binocular portions were included for analysis.

[00264] Mice were anesthetized with Nembutal (100 mg/kg), decapitated and the skull opened. A micro blade was used to remove a small core of tissue from the visual cortex of the appropriate hemisphere. Total RNA was extracted and purified, according to the instructions in the "Eukaryotic Target Preparation" manual available on the Affymetrix website. Fragmented, biotinylated cRNA was hybridized to the Affymetrix mouse genome U74v2 GeneChip set, which contains oligonucleotides that correspond to a total of 36,902 probes targeting genes and expressed sequence tags (ESTs) (Affymetrix). Array processing (hybridization, washing, staining and scanning) was performed by the Biopolymer Laboratory at MIT following standard Affymetrix protocols. A global scaling algorithm was used to normalize the expression level data from all samples.

[00265] In additional experiments in which the effects of short-term (4 days from P23-27) MD were investigated, as well the effects of IGF1 infusion concurrent with MD, a total of four experimental groups were analyzed: a new group of control animals (3 samples), the ipsilateral and the contralateral cortex of mice monocularly deprived for four days (3 samples

for the ipsilateral and 3 samples for the contralateral cortex), the contralateral cortex of mice that were monocularly deprived for four days and were injected IP daily with IGF1 solution (3 samples). Tissue was removed and the RNA extracted as described above, and labeled RNA was hybridized to the Affymetrix mouse genome 430.2 chip, which contains oligonucleotides that correspond to a total of 42,000 probes targeting genes and ESTs.

Data Analysis

[00266] *Significance analysis of microarrays*

[00267] A method for the Significance Analysis of Microarrays to assess changes in gene expression was used[31], and the method was implemented in MATLAB (The Mathworks, Natick, MA). The method allows the comparison of the expression level of each gene under two conditions (*e.g.*, MD vs. control; or DR vs. control). Under the null hypothesis that there are no changes in expression, the output is a probability of observing the given differences by chance (obtained by shuffling the data from the two conditions). Results of this analysis were compared against those obtained by setting a fixed threshold on the minimum intensity of each gene and a minimum ratio of expression between the two conditions. Correlations between replicates were calculated as correlation coefficients (c.c.) for all conditions: control (c.c.= 0.99 ± 0.002), MD 16 days (c.c.= 0.9 ± 0.05) , MD 4 days contralateral (c.c.= 0.99 ± 0.001), MD 4 days ipsilateral (0.99 ± 0.005), MD 4 days contralateral plus IGF1 (c.c.= 0.99 ± 0.004).

[00268] *GO annotations*

[00269] For the first set of experiments, Gene Ontology (GO) annotations were retrieved for each of the genes (http://www.geneontology.org/). Mapping of each Affymetrix probe to gene names was done using the annotations from Affymetrix (http://www.affymetrix.com/). GO provides information about the molecular function of a given gene (*e.g.* nucleic acid binding, ion transporter activity, *etc.*), the biological processes in which is involved (*e.g.* cell growth, cell communication), and the cellular location (*e.g.* nucleus, cytoplasm, *etc.*). For each of these organizing principles, GO provides a list of different categories to which each gene may be assigned. FatiGO[32] was used to identify categories for biological functions that are over- or under-represented in the different protocols of visual input deprivation.

Semi-quantitative RT-PCR

[00270] RNA was extracted as described above and cDNA was obtained with the Superscript First-Strand Synthesis System for RT-PCR (Invitrogen). PCR was performed according to the Invitrogen instruction manual. For each sample, PCR was run for the selected molecules and for Glycerol Phosphate Dehydrogenase (GPDH) as a control. PCR products were stained with ethidium bromide and run on an agarose gel. The intensity of each band was evaluated with ImageJ software (http://rsb.info.nih.gov/ij/) and normalized by the level of GPDH expression.

Results

[00271] DNA microarrays were used to examine large scale changes in gene expression in the V1 region of the cortex following dark-rearing (DR) and monocular deprivation (MD), using quantitative analyses of single genes as well as computational analyses of gene network activation (Fig. 1A). Mice used for microarray analyses of long-term visual deprivation were: (a) DR animals reared in complete darkness from birth till P27, the peak of the critical period for ocular dominance plasticity in mice[28], (b) MD animals which had one eyelid sutured from before eye-opening (at P11-12) through P27, and (c) P27 control animals, reared in standard conditions (Fig. 1A). The time course of the deprivation protocols was chosen to ensure as comparable periods of deprivation as possible in the DR and MD conditions – that is, starting at birth and continuing till P27. V1 was identified by stereotaxic coordinates and its location confirmed with both optical imaging of intrinsic signals[29] and by retrograde labeling of cells in the lateral geniculate nucleus (LGN) from injections of Alexa-CTB made in cortex[30]. RNA was extracted from V1 and hybridized to microarrays (Affymetrix). First, the expression level of gene transcripts was compared between control and deprived animals using a procedure for the Significance Analysis of Microarrays[31] (Fig. 1B, C). Two lists of genes were obtained for each deprivation protocol: those that were up-regulated in the deprived conditions versus control (1930 genes: 1730 genes up-regulated after DR and 200 genes up-regulated after MD), and those which were down-regulated in the deprived conditions versus control (1381 genes: 950 genes down-regulated after DR and 431 genes down-regulated after MD; Fig. 1D). The complete list of significantly ($P \leq 0.01$) up- and down-regulated genes is reported in tables for each experiment at (http://ramonycajal.mit.edu/kreiman/resources/v1plasticity/) and in Tables 4-9 herein (presented in the Appendix).

[00272] The Gene Ontology (GO) database[32,33] was used to group differentially expressed genes according to the biological processes in which they are involved. Of the 3311 differentially expressed genes in visually deprived groups, 1227 have known functions and have been reported in GO categories (level 3) for general biological processes. This analysis showed that some biological processes are common to both deprivation conditions, whereas others are differentially, or even exclusively, represented in one condition or the other.

[00273] For instance, genes implicated in "metabolism" and "cell communication" were upregulated in both conditions, with a stronger representation in DR cortex. At the same time, genes implicated in "cell motility" and "cell growth and maintenance" were primarily upregulated after DR. On the other hand, genes comprising "cellular physiological processes" and "organismal physiological processes" were primarily upregulated after MD. This overview suggested that while some similar mechanisms underlie the two forms of deprivation, distinct cellular processes may also be implicated in the two conditions.

[00274] To analyze the distinction further, a more detailed examination of genes encoding glutamatergic and GABA receptors was performed, including subunits of NMDA, AMPA and metabotropic glutamate receptors and subunits of GABA-A and GABA-B receptors. Table 1 shows changes in the expression of different subunits of GABA and glutamate receptors in MD and DR. "+" indicates a significant (two tailed t test $P \leq 0.05$) increase in the mRNA level in the deprived condition relative to control; "=" indicates no significant change. No gene was downregulated after deprivation relative to control.

Receptor	MD	DR
GluR1	=	+
GluR2	+	+
GluR3	+	+
NMDA1	=	+
NMDA2A	=	+
NMDA2B	=	+
NMDA2C	=	=
NMDA2D	=	=
mGluR3	=	=
mGluR5	=	=
mGluR8	=	=
GABAAα1	=	+
GABAAα2	+	+
GABAAα3	+	+
GABAAα4	=	+
GABAAα6	+	=
GABAAβ1	+	+
GABAAβ2	=	+
GABAAβ3	+	+
GABAAγ1	=	=
GABAAγ2	=	+
GABAAγ3	=	=
GABAAδ	=	=
GABAAε	=	=
GABAB1	=	=
GABACρ1	=	=
GABACρ2	=	=

[00275] This comparison of the main forms of excitatory and inhibitory transmission in the cortex showed that a substantial set of excitatory and inhibitory receptor genes was upregulated after DR. MD also upregulated both sets, but a smaller subset than DR (Fig. 2A). None of these receptor genes was downregulated after either form of deprivation. Thus, expression of both excitatory and inhibitory receptor genes is broadly upregulated in response to visual deprivation, but the response is stronger in the case of DR, where there is complete absence of light, than in the case of MD, where there is still visual stimulation through the closed eyelid though not in patterned form[34].

[00276] Several studies have reported that DR induces a delay in the maturation of inhibition[11,35,36]. No change in GAD65 expression was observed after DR or MD, but an

increase in GAD67 expression was observed after DR (Fig. 2B). More generally, a reduction was observed in expression of only one gene associated with cortical inhibitory neurons: all the probes associated with parvalbumin were downregulated after DR, whereas probes associated with other markers of inhibitory neurons[37,38], including calbindin, somatostatin, calretinin, cholecystokinin and neuropeptide Y, were either upregulated or did not change after DR (Fig. 2B). There was no change in any of these markers after MD (see also below, and Fig. 9). Thus, the functional reduction of inhibition and of inhibitory neurons after DR[36] is possibly mediated specifically by a reduction in the number of neurons expressing parvalbumin.

[00277] Next, the microarray expression levels of a subset of genes (Fig. 3A) were compared to an independent measure of gene expression using semi-quantitative RT-PCR performed on independent samples from those used for microarrays. The genes selected were significantly up-regulated (two-tailed t test $P<0.05$) in DR or MD cortex versus control, with at least a 1.5-fold greater expression after one or other form of deprivation. Furthermore, selected genes were in the top 5% in a list of probes rank-ordered by change in expression after DR or MD, based on calculation of the signal to noise ratio of each gene (from the mean microarray expression levels and standard deviations in deprived and control conditions). Analysis of representative genes that were upregulated after DR alone, after MD alone, or after both, is shown in Fig 3B,C. Genes upregulated after DR (but not MD) in the microarray data included molecules associated with synaptic structure and function, such as those involved in synapse formation (Neurexin1 and Synapsin 2), synaptic transmission mechanisms such as exocytosis (Synaptotagmin 1), neurotransmitter receptors (GluR1), and calcium-activated signaling (CaMKIIα and CREB). Changes observed with RT-PCR were consistent with the observations from the microarray data. That is, an increase in the expression of these molecules in the DR cortex was observed, and there was a greater increase in the DR condition compared to MD for each of them.

[00278] Fewer genes were up-regulated after MD (but not DR) compared to control, and they included molecules that are usually implicated in cellular pathology, including carcinogenesis (the DEAD-box RNA helicase DDX6[39]) and degeneration (Signal Transducers and Activators of Transcription 1, STAT1 – see below), or are activated by seizure (CaMKIIδ[40]). These genes also showed greater expression in the RT-PCR analysis. Finally, genes that were upregulated after both DR and MD included molecules associated with synaptic activity (GluR3 and GABA-Aα2), as well as molecules associated with neuronal growth and reorganization of connections (Insulin-like Growth Factor Binding

Protein 5, IGFBP5 – see below), and aspects of brain development (Nuclear Factor IB, NfiB[41-43]). In all of these instances, relative expression levels measured with RT-PCR were consistent with the microarray expression levels. Overall, these data suggest increased activation of a wide range of synaptic and neuronal mechanisms in V1 of DR animals, and to a lesser extent in MD animals, compared to control animals. Conversely, they suggest an increased activation of neuronal growth and degeneration mechanisms in MD animals, and to a lesser extent in DR animals, compared to control animals.

[00279] While the effects of MD are pronounced in the long term, they are also significant in the short term[14-17]. To examine similarities and differences with the long (16 day) period of MD, a microarray analysis of a short (4 day) period of MD, from P23-27, was performed. Short-term MD led to changes in the expression of many more genes than long-term MD. About 50% of the genes that were up- or down-regulated after long-term MD were also altered in expression after short-term MD; the upregulated genes included DDX6, IGFBP5 and NFiB. Genes upregulated by long-term MD but not short-term MD included STAT1 and CaMKIIδ. While some genes associated with synaptic transmission (such as GluR1, GluR3 and GABA-Aα2) did not change after short-term MD, more transmission-related genes (such as Synapsin 2 and Synaptotagmin 1) were up- or down-regulated after short-term compared to long-term MD.

Example 2: Identification of Gene Sets and Pathways Enriched In Genes that are Differentially Regulated in Visual Deprivation Paradigms

Materials and Methods

[00280] Gene Set Enrichment Analysis (GSEA) considers even small variations in all the mRNA probes of a group of genes, thereby assessing the enrichment of the whole gene set, and is relevant for detecting modest but coordinated changes in the expression of groups of functionally related genes. Such an analysis has particular value when an increase in the activity of several genes in a set could be more important than the strong activation of a single gene in a molecular cascade. Furthermore, the genes in the set typically share some functional or structural properties. Different gene sets have different sizes (for example, the gene set "Channel-passive-transporter" has 238 probes, while the "IGF1 pathway" has 46 probes), and all the probes corresponding to a single gene are reported in each gene set. A

recent description of the method[44] was followed here; a more detailed description has now appeared[85].

[00281] Let ${}_S\mu_i$ denote the mean expression level across samples of probe i (i=1,...,N where N is the total number of probes) in condition S (where S = DR, MD or $control$) and let ${}_S\sigma_i$ denote the standard deviation across samples. For a given probe i, the signal to noise ratio (SNR) of the deprivation condition is defined with respect to the control. For example, for dark rearing, the SNR was defined as ${}_{DR}SNR_i = \frac{{}_{DR}\mu_i - {}_{control}\,\mu_i}{{}_{DR}\sigma_i - {}_{control}\,\sigma_i}$. Probes were ranked according to the SNR value yielding an ordered list $L=\{g_1,\ldots,g_N\}$.

[00282] Given a set $\boldsymbol{G}$ containing N_G probes it can be assessed whether *the set of probes* is significantly over- or under- represented in one of the deprivation conditions with respect to the control condition (irrespective of whether the expression of the individual probes changed significantly or not). A representative example illustrating the algorithm is shown in Figure 4A. The following two cumulative distribution functions are defined: $P_{hit}(i)$=proportion of genes in the set $\boldsymbol{G}$ that show a rank less than i ($P_{hit}(i) = \frac{\#[g_{(j\le i)} \in G]}{N_G}$) and $P_{miss}(i)$ = proportion of genes *outside* the set $\boldsymbol{G}$ that show a rank less than i ($P_{miss}(i) = \frac{\#[g_{(j\le i)} \notin G]}{N - N_G}$). The running enrichment score is defined as $RES(i)=P_{hit}(i)-P_{miss}(i)$ (Figure 4A, top) and is derived from the position or rank of the genes in the set (Figure 4A, bottom). The enrichment score ES is the maximum deviation from 0 of $RES(i)$. If the genes in the set are highly enriched in the deprivation condition and appear first in the ordered list L, then P_{hit} will grow faster with i than P_{miss} for initial values of i and this will lead to a high positive ES value. Conversely, if the genes in the set are under-expressed in the deprivation condition and do not appear at the beginning of the list L, then P_{miss} will grow faster with i than P_{hit} and this will lead to a high negative ES score. If the genes in the set are randomly distributed, then the ES will show a value close to 0. The statistical significance of a particular value of ES is assessed by comparing it with the null distribution obtained by randomly shuffling the condition labels (deprivation and control) for each probe (using 1,000 permutations).

[00283] The procedure just described was repeated for each gene set, obtaining an enrichment score and an enrichment probability value for each set. It is possible to define a set of genes based on several different criteria. Here, sets of genes defined by common functional or structural properties in 3 specific biological databases were studied: BioCarta

(http://www.biocarta.com/), GenMapp (http://www.genmapp.org/), and GO (http://www.geneontology.org/). When a large number of gene sets is considered as in the present case, care should be taken because of the multiple comparisons involved and therefore the increased likelihood that one comparison will yield a significant result by chance. The multiple comparisons question was addressed here by controlling the Family Wise Error Rate[6]. To compare enrichment scores across gene sets, the enrichment scores are normalized by centering and scaling the ES using the mean and variance of each data, gene set pair. Throughout the text and in Tables 4 and 5, the normalized enrichment scores (NES) is shown for the gene sets enriched in dark rearing or monocular deprivation relative to control, or vice versa.

Results

[00284] Apart from the expression of individual genes, sets of genes that are linked together in specific functional pathways may be differentially expressed in DR and long-term MD and thereby lead to different cellular and molecular responses following the two forms of deprivation. To examine this possibility, a computational tool was used – Gene Set Enrichment Analysis (GSEA) – that considers the activation of sets of genes (such as cellular pathways, co-expressed genes, or genes in the same genomic locus) rather than the expression of a single transcript[44,45]. Thus, the extent to which a set of genes or a pathway is enriched in the deprivation paradigms was able to be measured with respect to control (or vice versa). 1374 pathways and gene sets taken from the following databases were considered: BioCarta, GenMapp, and GO. An example of the computation of the running and normalized enrichment score (NES) is shown in Fig. 4A for the ADP Ribosylation Factor (ARF) Pathway. The expression levels for the 19 probes in this pathway are shown in Fig. 4B. Qualitatively, Fig 4B shows that most of these probes were more highly expressed after MD than in control. Quantitatively, Fig. 4A shows that many of these probes were highly ranked in the rank-ordered set of MD probes, leading to a high running enrichment score for the ARF pathway. The gene sets with the highest scores in the deprived conditions versus control are listed in Table 2, which is a representation of the top Gene Sets enriched in DR (left column) and MD (right column) versus control. The Gene Sets are ranked according to their Normalized Enrichment Score. Gene Sets that are enriched in both conditions are shown with light shading. A star indicates that at least one probe of the correspondent Gene Set has been confirmed with RT-PCR. The gene sets with the highest scores in the control

versus deprived conditions (*i.e.*, are downregulated after deprivation) are listed in Table 3. The Gene Sets are ranked according to their Normalized Enrichment Score.

Table 3

	C>DR	NES	C>MD	NES
1	Neuropeptide_hormone	-17.0	20S_core_proteasome_complex	-5.3
2	Gas_exchange	-14.3	Ribosome	-4.6
3	Scavenger_receptor	-13.1	Circulation	-4.0
4	Serine_type_endopeptidase	-12.8	NADH_dehydrogenase	-4.0
5	Enzyme_binding_activity	-12.6	NADH_dehydrogenase_ubiquinone_activity	-3.8
6	Spliceosomal_subunit	-10.1	Endopeptidase_activity	-3.6
7	chr4q21	-9.1	Structural_constituent_of_ribosome	-3.2

[00285] These pathways were all significantly enriched (permutation test, $P<0.0001$) within the data set, based on a statistical comparison of enrichment scores obtained with 1000 randomly permutated gene sets. The GSEA method revealed quantitatively that different gene sets were preferentially activated after DR and MD. For example, the top enriched gene sets after DR included those involved in cellular activity, encompassing both metabolism related pathways (such as "metabolism" and "growth hormone pathway"), and synaptic activity related networks (such as "channel passive transporter," "vesicle-coat-protein," and "secretory vesicles"). After MD, however, the majority of the top enriched gene sets corresponded to pathways activated by growth factors ("epidermal growth factor," "insulin-like growth factor 1," and "platelet derived growth factor") and neuronal remodeling and degeneration ("nuclear factor of activated T cells," "JAK-STAT cascade," and "embryogenesis and morphogenesis"). Several gene sets were enriched in both conditions but were ranked in a different order confirming that common processes are also shared between the two conditions.

Table 2

	DR>C		NES	MD>C		NES
1	Channel_passive_transporter	★	27.3	egfPathway	★	16.4
2	Metabolism		25.6	igf1Pathway	★	9.7
3	mapkPathway	★	22.6	EGF_receptor_signaling_pathway		9.5
4	Vesicle_coat_protein		21.6	pdgfPathway	★	8.7
5	chr14q31		21.0	Embryogenesis_and_morphogenesis		8.0
6	ghPathway		20.0	Helicase_activity	★	7.9
7	chr8p12		18.8	tpoPathway	★	7.6
8	Secretory_vesicles	★	18.6	nfatPathway	★	7.5
9	chr20p12		17.8	Monocyte_AD_pathway		7.0
10	Apoptosis_regulator_activity		17.6	arfPathway		6.8
11	Protein_amino_acid_phosphorylation		17.4	JAK_STAT_cascade	★	6.7
12	chr4q12		17.3	Differentiation_in_PC12	★	6.6
13	rarrxrPathway		17.1	Channel_passive_transporter	★	6.4
14	ATPase_activity		17.0	tcrPathway	★	6.2
15	chr5q33	★	16.8	Transmembrane_RPTP		6.0
16	insulinPathway		16.8	ghPathway	★	5.8
17	Neurotransmitter_secretion	★	16.6	Inositolphosphatidylinositol_kinase_activity		5.6
18	edg1Pathway		16.6	keratinocytePathway		5.6
19	egfPathway		16.5	at1rPathway	★	5.6
20	RAS_protein_signal_transduction		16.5	gleevecPathway	★	5.6
21	Telomerase_dependent_telomere_maintenance		16.4	ngfPathway		5.5
22	Endoplasmic_reticulum	★	16.0	il2rbPathway		5.5
23	par1Pathway		15.6	Cancer_related_testis	★	5.5
24	ngfPathway		15.4	Adrenergic		5.4
25	at1rPathway	★	15.3	il7Pathway		5.3
26	Cancer_related_testis		15.3	il2Pathway	★	5.3
27	erk5Pathway	★	15.2	Dag1		5.3
28	JNK_MAPK_pathway		15.1	G_alpha_5_pathway	★	5.2
29	chr15q22		15.0	PTEN_pathway		5.2
30	Ngvm_c8		15.0	cblPathway		5.1
31	arenrf2Pathway	★	14.9	B_cell_receptor_complexes		5.0
32	Microtubule_binding_activity		14.9	p53_signalling		5.0
33	arfPathway		14.7	arenrf2Pathway	★	4.9
34	Potassium_ion_transport	★	14.5	chr20p12		4.8
35	mtorPathway		14.4	pitx2Pathway		4.8
36	crebPathway	★	14.3	igf1rPathway		4.8
37	gleevecPathway		14.3	hdacPathway	★	4.7
38	Protein_amino_acid_dephosphorylation		14.3	ccr5Pathway	★	4.7
39	myosinPathway		14.3	Insoluble_fraction		4.6
40	pdgfPathway		14.1	Granule_cell_survival	★	4.4
41	Ngvm_c32	★	14.0	35_cyclic_nucleotide_phosphodiesterase_activity		4.4
42	Microtubule_associated_complex		14.0	hivnefPathway		4.3
43	Neuronal_transmission	★	13.9	GPI_anchored_membrane_bound_receptor		4.2
44	erkPathway		13.6	Positive_regulation_of_transcription		4.2
45	CD40_pathway_map	★	13.6	tnfr1Pathway		4.2
46	Wnt_Signaling		13.6	Neuronal_transmission	★	4.2
47	Ion_transporter_activity		13.5	Transmembrane_RTK_signalling		4.1
48	Calmodulin_binding_activity	★	13.3	Synaptic_transmission	★	4.1
49	GPCR_pathway		13.1	spryPathway		4.1
50	chr2p22		13.1	Golgi		4.0

[00286] The genes previously identified with RT-PCR as highly expressed after DR or MD were also present in specific gene sets with high NES values (corresponding gene sets are marked), indicating that highly expressed genes together enrich specific pathways or networks of activation. The distribution of positive NES values for the DR versus control comparison is shown in Fig. 4C, which also shows the running enrichment scores for two pathways containing the molecules Creb and GluR1, respectively. The NES distribution for the MD versus control comparison is shown in Fig. 4D, together with the running enrichment scores for two pathways containing the molecules STAT1 and IGFBP5/IGF1, respectively. Each of these genes appears early in the rank-ordered set of DR or MD genes (*i.e.*, is one of the top enriched genes in the set and contributes significantly to the running enrichment score shown in Fig. 4C, D). Indeed, individual pathways often contain a number of genes that are implicated in DR or MD. Conversely, individual genes are often included in multiple pathways enriched after DR or MD. Many genes are common between the two deprivation conditions, as expected, but several are different (cf. Fig. 3). Considering the 100 most enriched gene sets in deprivation conditions, 1928 probes are present in DR but not MD gene sets, 1590 probes are present in MD but not DR gene sets, and 2361 probes are present in both MD and DR gene sets.

Example 3: Expression of Selected Proteins Encoded by Differentially Expressed Genes

Materials and Methods

Immunohistochemistry

[00287] Mice were anesthetized and transcardially perfused with a solution of 4% paraformaldehyde. The appropriate brain hemispheres were removed and equilibrated in 30% sucrose in PBS. Coronal sections containing visual cortex were cut using a freezing microtome. Immunohistochemistry for GluR1 (1:500, Upstate), IGFBP5 (1:500, USBiological), CaMK2alpha (1:500, Sigma), PhosphoCREB (1:500, Cell Signaling), activated Stat1(1:500, Abcam), parvalbumin (1:1000, Chemicon), calretinin (1:500, Chemicon), somatostatin (1:300, Chemicon), neuropeptideY (1:400, Chemicon), synapsin 1 (1: 500, Chemicon), IGF1 (1:250, Chemicon), GAD 67 (1:400, Chemicon), IGF1R (1:500, Upstate), PI3K – catalytic subunit 110 (1:400, Upstate), phosphorylated-Akt (1:250, Cell Signaling), was carried out as described elsewhere[82,83]. For each staining, analysis was

repeated in parallel for control and deprived animals. Experiments were carried out at least on two animals for each group and repeated twice. The intensity of staining in sections from control and deprived animals was evaluated with ImageJ software (http://rsb.info.nih.gov/ij/). Counts of parvalbumin, calretinin, somatostatin and NPY-positive cells were performed as described elsewhere[29].

Results

[00288] The results described thus far represent information at the mRNA level. Given that multiple control mechanisms can exert their actions after the transcriptional stage, analysis of protein expression is can be used to confirm the functional activation of a pathway beyond RNA analyses. To further examine the regulation of the genes described above and their associated pathways, the expression of their proteins was analyzed using immunohistochemistry.

[00289] First, markers were examined for selected classes of interneurons. Since all the microarray probes for parvalbumin were downregulated after DR (Fig. 2B) while other interneuron markers remained unchanged or increased, it was determined whether a similar pattern were reflected in the number of neurons that were immuno-positive for these markers. A significant decrease (by 40%, $p<0.01$) in the number of parvalbumin-positive neurons in DR relative to control animals (Fig. 5A) was observed, while calretinin-positive neurons remained unaltered and the number of neurons positive for somatostatin and neuropeptide Y increased ($P< 0.05$). For all the antibodies examined, there was no effect of MD on the number of stained neurons. Thus, the reported effect of DR as delaying inhibition is likely due to a delay in the development of neurons that express parvalbumin.

[00290] Following up the highly enriched gene sets after DR, the expression of GluR1 (Fig. 5B) phospho-CREB (Fig. 5C), and CaMKIIα were examined, present in the "CREB pathway" gene set. Each of these molecules was over-expressed in V1 of DR animals compared to control, consistent with previous reports of the involvement of CaMKIIα in DR[46], of GluR1 as a substrate for CaMKIIα expression[47], and of CREB-mediated gene expression as related to the maturation of the visual cortex[48]. Similarly, following MD, two novel proteins were examined, activated STAT1 and IGFBP5, which are constituents of highly enriched gene sets, though neither has been previously implicated in the cortical effects of MD or any form of visual deprivation. STAT proteins are phosphorylated by Janus Kinases (JAK); the JAK-STAT cascade is usually activated in response to cytokine signaling,

but is also upregulated in response to nerve injury and ischemia[49-51]. Immunostaining for the phosphorylated form of STAT1, indicating activation of the JAK-STAT cascade, showed that the molecule was significantly upregulated in V1 after MD (Fig. 5D). IGFBP5 is widely expressed in the brain[52] and binds IGF1, a peptide that is genetically related to insulin[5354,55]. IGFBP5 expression was significantly upregulated in V1 after long-term MD (Fig. 5E).

Example 4: Administration of IGF1 Counteracts Effects of Monocular Deprivation

Materials and Methods

Monocular Deprivation

[00291] For monocular deprivation, animals were anesthetized with avertin (0.016 ml/g) and the eyelids of one eye were sutured (at P20-22 for 7 days for imaging experiments). Before imaging, the suture was removed and the deprived eye re-opened. Only animals in which the deprivation sutures were intact and the condition of the deprived eye appeared healthy were used for the imaging session. For DR animals (aged P27-30), the procedure was the same described above, with the exception that the animals were anesthetized in darkness and not exposed to light until deeply anaesthetized; in these mice only the binocular response was evaluated and compared to that in control animals.

Optical imaging of V1

[00292] Mice (129/SvEv and C57Bl/6) aged P26-30 were anesthetized with urethane (1.5 g/Kg) and chlorprothixene (0.2 mg), as described[84]. Skin was excised and the skull exposed over V1. A custom-made attachment was used to fix the head and minimize movements. The cortex was covered with agarose solution (1.5 %) and a glass cover slip. During the imaging session the animal's body temperature was kept constant with a heating blanket and the EKG monitored constantly. Eyes were periodically treated with silicone oil and the animal allowed to breathe pure oxygen. Red light (630 nm) was used to illuminate the cortical surface, and the change of luminance was captured by a CCD camera (Cascade 512B, Roper Scientific) during the presentation of visual stimuli (STIM, Optical Imaging). Custom software was developed to control the image acquisition and synchronization between the camera and stimuli. An elongated horizontal or vertical white bar (9° x 72°) over a uniformly gray background was drifted continuously through the up-down or peripheral-central

dimension of the visual field. After moving to the last position, the bar would jump back to the initial position and start another cycle of movement – thus, the chosen region of visual space (72° x 72°) was stimulated in periodic fashion (9 sec/cycle). Images of visual cortex were continuously captured at the rate of 15 frames/sec during each stimulus session of 25 minutes. Four sets of stimuli (upward, downward, leftward, rightward) were randomly presented to either eye monocularly or both eyes simultaneously.

[00293] A temporal high pass filter (135 frames) was employed to remove slow noise components, after which the temporal Fast Fourier Transform (FFT) component at the stimulus frequency (9 sec^{-1}) was calculated pixel by pixel from the whole set of images. No spatial averaging was done. The amplitude of the FFT component was used to measure the strength of visually driven response for each eye, and the ocular dominance index was derived from each eye's response (R) at each pixel as ODI = (Rcontra – Ripsi)/ (Rcontra + Ripsi). The binocular zone was defined as the region with equivalent driving from both eyes.

<u>IGF1 Treatment</u>

[00294] For IGF1 treatment, a solution containing GPE, the functional peptide of IGF1, was prepared as described[56]: 300 μg of GPE was injected intra-peritoneally daily for the entire period of deprivation. This peptide is referred to as "IGF1" in the Results below.

Results

[00295] IGFBP5 is one of the most upregulated genes after MD, with one of the highest mRNA expression levels after RT-PCR, and the highest differential level of protein expression after MD or DR. Furthermore,.the IGF1 pathway is one of the top enriched pathways after MD in the GSEA, and both IGFBP5 and IGF1 are constituents of several highly enriched pathways after MD. The present invention encompasses the recognition that the upregulation of IGFBP5 following MD could imply a competitive role for IGF1 in mediating ocular dominance plasticity after MD, and that exogenous application of IGF1 could then prevent the effect of MD (see, for example, ref. 56). The possible functional involvement of the IGF1/IGFBP5 system in experience-dependent plasticity in visual or any cortex has not been examined to date. Thus, the physiological effects of IGF1 administration on ocular dominance plasticity in V1 were determined *in vivo* (Fig. 6).

[00296] IGF1 is able to cross the blood brain barrier[56], thus, intra-peritoneal administration of IGF1 prevents the effects of ischemia in the CNS[57]. Optical imaging of intrinsic signals was used to evaluate the strength of signals from each eye in the physiologically identified binocular portion of V1 (Fig. 6A). Imaging was performed on three age-matched groups of mice during the critical period: control animals (n=3), animals monocularly deprived for 7 days (n=4), and MD animals with IGF1 delivered intraperitoneally during the period of deprivation (n=3). Fig. 6B shows the ocular dominance distribution of pixels within the binocular zone in individual control, MD and MD + IGF1 animals. The pixel distribution in control mice favored the contralateral eye, as described previously with single unit recordings[28] and visual evoked potentials[58]. Suturing the contralateral eye caused the ocular dominance distribution to shift towards the open, ipsilateral, eye. Simultaneous administration of IGF1 prevented the ocular dominance shift towards the open eye. A comparison of the mean ocular dominance index across the population of animals (Fig. 6C) showed that deprivation of the contralateral eye shifted the index significantly relative to control animals ($P<0.05$, treating each animal as a single datum), whereas MD combined with administration of IGF1 prevented the shift ($P>0.2$).

[00297] The mechanisms of IGF1/IGFBP5 action were investigated by asking if specific cell types and proteins were associated with the pathway. To clarify whether IGFBP5 is expressed in excitatory or inhibitory neurons, a double immunostaining for IGFBP5 and GAD67 was performed, and IGFBP5 was shown to be expressed in a range of neurons - not exclusively in inhibitory interneurons (Fig. 7A). Next the expression in V1 of several molecules involved in IGF1 signaling[53,59] was assayed by immunostaining after MD alone and after MD with concurrent delivery of IGF1 (Fig. 7B). IGFBP5 immunostaining showed a significant increase after short-term MD, and no change from normal levels in short-term MD animals that also received IGF1 during the deprivation period (MD + IGF1). Expression of the IGF1 receptor (IGF1R), on the other hand, was significantly down-regulated after MD, and expression was partially restored in MD+IGF1 animals. Phosphatidylinositol 3-Kinase (PI3K), which is activated by IGF1, was significantly diminished in expression after MD but was fully restored after MD + IGF1 treatment ($P<0.05$ for both comparisons; Fig. 7B).

[00298] Expression of one of the substrates of PI3K, phosphorylated-Akt, was significantly reduced by MD and restored by addition of IGF1. Because IGF1 and PI3K signaling have been related to neuronal transmission[60-62], changes in synaptic activity were screened for by immunostaining for synapsin 1. The level of synapsin expression did not change significantly in MD animals versus control, but MD + IGF1 animals showed a

significant increase ($P < 0.05$). Finally, a microarray analysis of MD + IGF1 animals was performed for comparison with MD animals, to examine genes that might be differentially regulated by IGF1 and hence be associated specifically with IGF1 mechanisms. Expression of only a small fraction of genes was significantly altered in MD + IGF1 animals compared to MD animals (see Tables 10 and 11). Adding IGF1 significantly downregulated IGFBP5 and upregulated PI3K compared to MD alone ($P<0.01$). Thus, PI3K appears to be an important signal downstream of IGF1 in mediating ocular dominance plasticity.

Example 5: Release of a Plasticity-Modifying Agent from Hydrogel Discs

[00299] In order to demonstrate the release of a plasticity-modifying agent over time from a hydrogel matrix suitable for drug delivery, hydrogel discs containing various amounts of IGF1 are fabricated and subjected to incubation in a PBS solution, during which release of IGF1 is measured over time.

[00300] The hydrogel consists of a poly(ethylene glycol) (PEG) core with poly(lactic acid) (PLA) linkages (*i.e.*, it contains hPLA-b-PEG-PLA macromers) and has been previously described (Sawhney, *et al.*, 1993; and Burdick, *et al.*, 2002). In order to fabricate discs, the hydrogel macromer is combined with IFNγ and the photoinitiator 2-hydroxy-1-[4-(hydroxyethoxy)phenyl]-2-methyl-1-propanone, (Ciba-Geigy) in a PBS solution. The solution (50 μl) is placed into a mold of the desired dimensions and then crosslinked under UV light for 10 minutes to cause polymerization, thereby resulting in discs of hydrogel with dimensions of approximately 5 mm by 1 mm.

[00301] The hydrogel discs are placed in 0.5 ml of PBS solution and release is monitored over 14 days using an ELISA kit according to the manufacturer's directions. Three hydrogel discs are tested for each of the conditions (2 different loading doses each for single-chain and two-chain tPA), and the amount of tPA released was averaged at each time point. Data are analyzed to determine the relationship between IGF1 release and the amount of IGF1 present in the disc. The relationship allows for the control of the amount of IGF1 released by changing the amount of IGF1 initially loaded into the gel. The total amount of IGF1 released can be calculated from the concentrations and the fact that the discs are incubated in 0.5 ml PBS solution. This information can be used to determine the amount of IGF1 and the amount of hydrogel needed to deliver a desired dose over time.

Example 6: Effect of IGF1 on Recovery from Spinal Cord Injury

Materials and Methods

[00302] In a first set of experiments, 6 female Sprague-Dawley rats were anesthetized and spinal cord injury (SCI) was induced at T10 by using the New York University impactor with a 10 gm weight and a 12.5 mm weight drop. Behavioral tests were conducted on the first post-operative day and then weekly. The BBB (Basso, Beattie, Bresnahan) behavioral test was used to examine hind limb reflexes as well as coordinated use of the hind limbs (Basso *et al.*, 1995; and Basso, *et al.*, 1996). This "BBB" scale has been adopted by the Multicenter Animal Spinal Cord Injury Study and by other workers in the field. Therefore, use of the BBB as an outcome measure after experimental SCI supports easier interlaboratory comparison of results.

[00303] A second operation is conducted three days post-operatively at T8-T9 for a bolus micro-injection of 10 μg of IGF1 or GPE and, in some experiments, also 10 μg of tPA (human two-chain tissue plasminogen activator; American Diagnostica, Inc.) reconstituted from lyophilized powder to 10 μg/10 μL) into three of the six rats. Following the bolus injection, an osmotic minipump (Alzet Model 2002: 14 day pump; Durect Corp., Cupertino, CA) loaded with IGF1 or GPE and, in some experiments, also tPA (200 μL total volume, delivering 0.5 μl/hour, 10 μg IGF1 or GPE, and, in some experiments, 10 μg tPA/day) is implanted at the side of injury and delivered tPA for 10 consecutive days. At the 6th post-operative week, BDA and Fluorogold injections are made in cortex to assess the extent of corticospinal tract regrowth and reconnection, and at the 10th post-operative week, animals are perfused and their spinal cords were removed for histological analysis. Implanted minipumps are saved for analysis of IFG1 activity (and in some experiments tPA activity) in the remaining solution.

[00304] A second set of experiments is performed on a larger group of animals using the same techniques as the first except that Alzet Model 1007B:7 day pumps holding a total volume of 90 μl, infusing 0.5 μl/hour are used, and delivery continuesfor 7 days rather than 10.

[00305] In a third set of experiments, GPE is administered intraperitoneally at a range of different doses (10 μg – 1 mg) daily.

[00306] In a fourth set of experiments, GPE is administered intraperitoneally at a range of different doses (10 μg – 1 mg) daily and a pump delivering tPA is implanted as described above.

[00307] In all experiments, the extent of corticospinal tract regrowth and reconnection is evaluated and histology is performed. Anatomical analysis with hematoxylin and eosin staining is performed to evaluate the contusion site. Sections are stained with solvent blue [SB] / hematoxylin and eosin as described in Teng and Wrathall, 1997. The integrity of the residual white matter is assessed. For example, high quality myelin stain in the spared white matter demonstrates existence of myelinated axons.

[00308] Functional parameters are assessed. Pre-operatively, animals performance on the BBB test is expected to have a baseline value of 21. On the first post-operative day, all animals are expected to be significantly impaired on the BBB test, and their scores reduced to 0. After 10 weeks of recovery, control animals typically achieve a final score of about 2.5 on the BBB test while treated animals are expected to achieve a higher score, *e.g.*, a final score close to 9, which is considered significant improvement.

Example 7: Effect of IGF1 with or without tPA in an Animal Model of Stroke

[00309] Thirty rats are trained on a battery of behavioral tasks until they achieved an asymptotic level of competence. Rats then receive occlusion of the middle cerebral artery (MCAO) according to standard procedures. After recovery from surgery, the rats are significantly impaired on all of the behavioral tasks. At the time of MCAO surgery, 20 of the 30 rats are also implanted with an osmotic mini-pump (Alzet model 2001: 7 day pump with 90 μl total volume and 1.0 μl/hour infusion) for intraventricular infusion contralateral to the site of the MCAO. For 10 of the 20 rats, the mini-pumps are filled with IGF1 at 10 μg/day. For the other 10 rats the mini-pumps are filled with IGF1 at 10 μg/day and human two-chain tissue plasminogen activator (tPA; American Diagnostica, Inc.) at 10 μg/day. The other 10 rats receive daily intraperitoneal injections of GPE at a dose ranging from 10 μg to 10 mg, *e.g.*, 300 μg.

[00310] Treatment is initiated 2 days following MCAO and maintained for 7 days. Control and treated rats are subsequently tested weekly for behavioral recovery.

Equivalents and Scope

[00311] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention, described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

[00312] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

[00313] In the claims articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Thus, for example, reference to "a nanoparticle" includes a plurality of such nanoparticle, and reference to "the cell" includes reference to one or more cells known to those skilled in the art, and so forth. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process. Furthermore, it is to be understood that the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, descriptive terms, *etc.*, from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Furthermore, where the claims recite a composition, it is to be understood that methods of using the composition for any of the purposes disclosed herein are included, and methods of making the composition according to any of the methods of making disclosed herein or other methods known in the art are included, unless otherwise indicated or unless it would be evident to one of ordinary skill in the art that a contradiction or inconsistency would arise.

[00314] Where elements are presented as lists, *e.g.*, in Markush group format, it is to be understood that each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements, features, *etc.*, certain embodiments of the invention or aspects of the invention consist, or consist essentially

of, such elements, features, *etc.* For purposes of simplicity those embodiments have not been specifically set forth *in haec verba* herein. It is noted that the term "comprising" is intended to be open and permits the inclusion of additional elements or steps.

[00315] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[00316] In addition, it is to be understood that any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the compositions of the invention (*e.g.*, plasticity-modifying condition, any plasticity-modifying agent, any proteolysis-enhancing agent, any active agent, any drug delivery system, any mode of administration, any dosage regimen, any therapeutic application, *etc.*) can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

[00317] The publications discussed above and throughout the text are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior disclosure.

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Table 4

%Dark rearing versus control
%Downregulated in dark rearing
%Significance criterion = 0.01
%

%i	affyid	p	DR	control	gene		
1	116913_at	0.000013	839.37	1223.2	A630065K24Rik	AI853593	NM_144810
2	160625_f_at	0.000015	317.93	393.9	BC004636	AA048058	NM_145524
3	163279_at	0.000018	811.87	1345.03	BC033915	AW121881	NM_027498
4	116738_at	0.000026	2200.47	4218.77	3110031O14Rik	AI840706	XM_142154
5	100539_at	0.000028	2230.47	3377.33	2410041A17Rik	AI841279	NM_133348
6	101039_at	0.000029	703.03	1054.37	Col4a2	X04647	NM_009932
7	96244_at	0.000032	5196.07	5771.67	Uchl1	AB025313	NM_011670
8	96900_at	0.000034	5199.73	8428.83	1620401E04Rik	AW125480	NM_175329
9	111915_at	0.000044	428.83	708.43	1500003O22Rik	AI585944	NM_025897
10	164133_at	0.000044	2202.27	2806.9	Trim9	AI845772	---
11	166936_i_at	0.000044	584.2	964.9	BC004091	AV214573	NM_178408
12	114451_at	0.000049	1478.97	2237.73	---	AI848332	NM_001024927
13	112460_at	0.00005	1695.03	2404.8	3010021M21Rik	AW121562	NM_180600
14	111941_at	0.000053	810.07	1369.87	Snx16	AW046222	NM_029068
15	104738_at	0.000063	505.23	903.83	Zrf2	D63784	NM_009583 /// NM_009584
16	106175_at	0.00007	3470.03	6281.83	---	AI851974	---
17	93312_at	0.000074	1795.4	2625.2	Ube2g1	AW124623	NM_025985
18	106279_at	0.000074	549.4	1024.7	2810004N20Rik	AI847372	NM_025576
19	92987_at	0.000075	2622.93	4105.5	Slc4a3	M28383	NM_009208
20	103904_at	0.000077	813.33	2163.97	Krt2-8	X81584	NM_008344
21	162605_at	0.00008	282.6	349.33	AI449175	AI851371	NM_172754
22	115062_at	0.000081	655.2	975.6	Rev1l	AW122118	NM_019570
23	105133_at	0.000084	562.33	1133.57	---	AW048077	---
24	93984_at	0.000086	4129.97	6006.23	Atpi	AF002718	NM_007512
25	103234_at	0.000088	626.73	769.43	---	M35131	NM_010904
26	110406_at	0.000094	476.13	700.7	---	AA958839	XM_620663
27	104195_at	0.000096	96.9	276	5730408K05Rik	AA939440	---
28	105788_at	0.000102	2938	4379.33	9630017H13	AI837651	NM_001001160
29	103855_at	0.000111	230.83	408	---	AW123286	NM_011117 /// NM_201385 /// NM_201386 /// NM_201387 /// NM_201388 /// NM_201389 /// NM_201390 /// NM_201391 /// NM_201392 /// NM_201393 /// NM_201394
30	160072_at	0.000111	134.3	174.2	Rfc3	AV026570	XM_132528
31	161077_f_at	0.000118	184.17	280.43	Smarcd2	AV252495	NM_031878
32	160704_at	0.00012	439.93	643.23	1110067D22Rik	AW121603	NM_173752

Table 4

33	94875_at	0.000124	371.97	646.6	Mrpl20	AI838915	NM_025570
34	165290_f_at	0.000127	203.73	398.97	---	AV229080	NM_021414
35	103910_at	0.000128	585.83	1028.43	---	AJ249987	NM_020024
36	114032_f_at	0.000129	4244.37	7428.33	Glcci1	AI843759	NM_133236 /// NM_178072
37	116058_at	0.000139	313.97	485.83	2900057K09Rik	AI854413	---
38	168299_f_at	0.000143	491.27	1205.07	---	AV090198	---
39	107599_at	0.000146	804.63	1145.87	---	AI121363	XM_148990
40	164029_at	0.000148	533.3	770.33	DXImx41e	AI891531	NM_173747
41	109727_at	0.000154	923.97	1367.5	Phf2	AI851684	NM_011078
42	93288_at	0.000166	2777.13	4956.27	Arpc2	AI835883	XM_129773
43	112908_at	0.000168	490.73	1025.87	Axud1	AI849021	NM_153287
44	164429_f_at	0.000172	1055.9	1682.4	---	AV086748	NM_018819
45	161818_f_at	0.000174	279.57	467.5	Pdcd4	AV376445	NM_007607
46	161357_r_at	0.00019	509.57	987.2	---	AV207739	NM_008183
47	162702_at	0.000196	2757.77	3821.47	Dusp14	AI851272	NM_019819
48	139276_at	0.000196	1168.13	1923.77	---	AW046131	XM_127272
49	160235_at	0.000197	460.4	862.2	5033425B17Rik	AI843521	NM_027215
50	160423_at	0.0002	243.13	356.23	Mrps2	AI853575	NM_080452
51	115269_at	0.000216	436.47	856.27	Bin3	AI155952	XM_358314
52	105832_at	0.000217	561.37	985	---	AI849717	NM_030743
53	163675_r_at	0.000219	88.13	191.97	Nr4a2	AW045923	---
54	94536_s_at	0.000222	3045.97	3845.37	2900073G15Rik	AI843417	NM_023402 /// NM_026064
55	169396_r_at	0.000226	1919.97	3561.6	---	AV101367	XM_132830
56	102870_at	0.000227	4815.7	10976.93	5930418K15Rik	AW125272	NM_001033178
57	111564_at	0.000244	422.17	650.93	---	AA067741	XM_484476
58	162762_at	0.000257	1108.8	1805.77	---	AW122369	NM_001001881
59	161073_at	0.000289	1949.23	2721.17	C630002B14Rik	AI846304	NM_175331
60	165219_s_at	0.000293	467.13	588.8	---	AV364901	NM_021890
61	162608_at	0.000294	136.8	247.8	---	AI844245	NM_025426
62	92981_at	0.000304	1245.53	1964.63	---	X68837	NM_009129
63	162486_f_at	0.000308	538.8	635.9	---	AV122030	NM_007834
64	165073_f_at	0.000317	307.4	592.13	---	AV335734	NM_153515
65	101101_at	0.000324	1740.1	2329.1	Ppp2cb	Z67746	NM_017374
66	170060_r_at	0.000324	4751.67	7112.73	Hoxa11s	AV305600	NM_010450
67	98106_at	0.000327	420.03	537.5	Timm44	U69898	NM_011592
68	102773_at	0.000333	156.93	226.7	Car8	X61397	NM_007592
69	100084_at	0.000335	477.63	680.03	Vil2	X60671	NM_009510
70	161998_f_at	0.000335	1073.2	1751.13	---	AV329719	NM_145602

Table 4

71	95044_at	0.000338	721.07	1096.03	1500003D12Rik	AI844549	NM_025895
72	103346_at	0.000347	509.33	675.37	Clk2	AF033564	NM_007712
73	160487_at	0.000362	268.33	601.83	Myl4	M19436	NM_010858
74	93686_s_at	0.000372	6.97	87.07	Cit	AF086824	NM_007708
75	108512_at	0.000389	640.5	890.87	2810038K19Rik	AW125356	NM_023684
76	114832_at	0.000391	376	829.4	BC023296	AI197451	NM_153545
77	101947_at	0.000393	539.83	1103.2	Nakap95	AB028921	NM_017476
78	160442_at	0.000399	369.77	494.43	Cct2	AB022156	NM_007636
79	163701_at	0.000404	684.77	1033.6	1500041J02Rik	AI835985	NM_026424
80	102134_f_at	0.000408	490.67	800.53	Atp5g2	AI461702	NM_026468 /// XM_620687
81	102194_at	0.000411	510.17	770.07	2810432D09Rik	AW122332	NM_027278
82	110124_at	0.000417	275.37	356.17	6430573D20Rik	AI647471	NM_172689
83	171609_r_at	0.000417	14280.63	18180.93	AV168074	---	
84	94915_at	0.000437	582.97	820.77	Ppib	X58990	NM_011149
85	115131_at	0.000437	1635.73	2110.27	8430419L09Rik	AW045203	NM_028982
86	106830_at	0.000437	807.83	1624.13	Arhgef7	AW045717	NM_017402
87	103531_f_at	0.000438	260.8	366.4	---	AI049144	NM_026184
88	97274_at	0.000439	877.3	1346.67	Psmd14	Y13071	NM_021526
89	162928_f_at	0.00044	8255.73	12307.2	Cdk5r	AI852396	NM_009871
90	99640_at	0.000452	803.83	1170.6	Minpp1	AW045481	NM_010799
91	94796_at	0.000457	1368.6	3329.33	Psmd11	AA710643	---
92	114994_at	0.000457	1628.73	2268.93	Rfx1	AW050047	NM_009055
93	98143_at	0.000458	524.7	691.4	Fut8	AB025198	NM_016893
94	134405_at	0.000462	3581.13	6639.93	Egr3	AI662230	NM_018781
95	161864_f_at	0.000466	437.9	586.5	---	AV068306	NM_008959
96	95940_f_at	0.000473	145.3	302.47	9830126M18	AW047237	NM_198301
97	114093_at	0.000483	813.27	1087.47	---	AI852806	XM_355470
98	103606_r_at	0.000484	288.93	652.93	Rgs19	AW121438	NM_026446
99	96060_at	0.000489	298.57	380.83	Serpinb6a	U25844	NM_009254
100	93500_at	0.000493	1358.53	1782.6	Alas1	M63245	NM_020559
101	92724_at	0.000507	134.27	201.67	Hnrpa1	AI183202	NM_010447
102	113337_at	0.000511	512.07	666.2	Miz1	AW121227	NM_008602
103	170481_at	0.000535	1800.4	2979.17	---	AV216614	---
104	112992_at	0.000536	509.1	678	4930402H24Rik	AI852138	NM_029432
105	109389_at	0.000544	152.13	281.97	4732460C16Rik	AW122048	---
106	110371_at	0.000547	507.83	858.9	D130064H19Rik	AA793751	NM_172593
107	161965_r_at	0.000551	712.77	1033.43	---	AV367494	NM_031878
108	99095_at	0.000557	376.67	678.7	Max	M63903	NM_008558

Table 4

109	160811_at	0.000561	253.23	344.5	MGC56855	AW121710	NM_177682
110	101023_f_at	0.000565	584.67	1180.13	---	AI843605	---
111	164293_at	0.000574	1032.37	1741.63	---	AV208915	NM_023374
112	166964_at	0.000579	772.4	1057.33	---	AV369443	NM_009120
113	93459_s_at	0.000587	763.43	1249.4	Fzd4	AW122897	NM_008055
114	94347_i_at	0.000588	440.73	569.03	Pcmt1	AW124044	NM_008786
115	100482_at	0.000589	723.1	1054.6	BC023040	AI836408	NM_183149
116	136675_at	0.000593	2127.93	3643.63	LOC328644	AI851743	NM_198629
117	165830_f_at	0.000596	796	1493.43	A330051M14Rik	AV250704	XM_130112
118	134734_at	0.000597	1421.67	2019.6	---	AI451645	---
119	164059_f_at	0.000613	1644.33	3213.6	Cntn1	AI425965	NM_007727
120	138479_at	0.000618	2799.5	4439.7	Camk1g	AW122501	NM_144817
121	116412_r_at	0.000622	143.47	375.4	---	AI850995	---
122	96709_at	0.000632	4858.37	7394.83	1110008P14Rik	AI839839	NM_198001
123	112416_at	0.000634	1732.87	2400.2	Ctdspl	AA607067	NM_133710
124	133702_at	0.000636	2357.53	3077.27	A430091O22Rik	AI462128	NM_183024
125	162645_at	0.00064	962.4	1352.07	Prkar2b	AI851427	NM_011158
126	92773_at	0.000647	124.07	186.47	Ier5	AF079528	NM_008737
127	102924_at	0.000648	1018	1414.97	Dtx1	U38252	NM_008052
128	160975_at	0.00065	268.9	525.47	4833417L20Rik	AI504338	NM_030179
129	108293_at	0.00065	1022.1	1608	Trim6	AI592230	NM_001013616
130	102742_g_at	0.000655	3248.87	7040.67	Mapt	M18775	NM_010838
131	109529_at	0.000657	939.07	2910.57	---	AW120726	---
132	161214_r_at	0.000661	912.63	1531.6	---	AV265258	NM_153161
133	164896_f_at	0.000681	810.3	1164.43	---	AV063259	NM_080469
134	160485_r_at	0.000691	455.87	820.2	Ywhae	D87663	NM_009536
135	111343_i_at	0.000697	1646.63	2301.37	2310047O13Rik	AI853582	NM_024185
136	112395_at	0.000698	143.63	208.67	8430405D05Rik	AW048395	XM_111053
137	106577_at	0.000706	4721.93	7922.53	Bteb1	AI849498	---
138	164383_f_at	0.000708	137.67	292.2	---	AV315810	NM_011809
139	117199_at	0.000719	361.33	511.2	---	AI891940	NM_023348
140	101074_at	0.000737	371	503	Ddost	D89063	NM_007838
141	162967_r_at	0.00074	3387.6	4645.53	3100002M17Rik	AI842784	NM_027016
142	135314_at	0.000745	4635.3	7655.5	---	AI842058	NR_002321 /// NR_002322
143	168181_i_at	0.000758	1397.83	2201.9	Rps3	AV169767	NM_012052
144	111421_at	0.000775	1711.43	2403.93	Sh3gl1	AW046845	NM_026530
145	135401_at	0.000784	1828.13	3334.33	---	AW214326	NM_011447
146	110360_at	0.000795	550.1	1219.3	3300001P08Rik	AI849146	NM_026313

Table 4

147	167055_f_at	0.00081	2927.7	6142.57	Mcl1	AV317016	NM_008562
148	168944_i_at	0.000814	3227.33	4783.9	---	AV077500	NM_024432
149	165357_f_at	0.000821	424.3	862.4	---	AV020220	NM_007748
150	92794_f_at	0.000822	887.27	1350.2	Nme1	M35970	NM_008704
151	93589_at	0.000834	1398.57	2411.53	Lysal1	AI851172	NM_026174
152	135609_at	0.000838	669.1	1052.17	Egln3	AI505553	NM_028133
153	96042_at	0.000857	359.77	539.2	Sod2	L35528	NM_013671
154	160727_at	0.000857	1075.83	1333.4	2410002F23Rik	AW046357	NM_025880
155	164148_at	0.000861	906.03	1939.1	Gtl2	AI834913	NM_144513
156	108029_at	0.000865	355.8	526.53	4931428D14Rik	AW125801	NM_025740
157	95759_at	0.000885	420.2	541.33	2900092E17Rik	AW123746	NM_030240
158	103959_at	0.000889	155	268.13	Phf13	AI605405	NM_172705
159	114069_at	0.00089	477.37	1067.17	---	AI844797	NM_001013390
160	109077_at	0.000897	943.67	1417.73	Ube3b	AI854538	NM_054093
161	108019_f_at	0.000902	581.7	878.47	Hmga1l4	AI850464	NM_023547
162	138517_at	0.000906	466.47	750.47	1700019B16Rik	AI847259	NM_028829
163	105580_at	0.000914	411.93	627.13	4930470D19Rik	AA517795	NM_026274
164	95387_f_at	0.000918	77.23	236.3	Sema4b	AA266467	NM_013659
165	93048_at	0.000919	583.17	925.33	Clpp	AJ005253	NM_017393
166	92202_g_at	0.000927	1126.27	2324.87	---	AI553024	XM_134826
167	171624_at	0.000928	77	237.93	AV161512	NM_009760	
168	164308_f_at	0.000934	643.03	963.67	---	AV239634	NM_019705
169	101078_at	0.000941	5107.2	6915.03	Bsg	Y16258	NM_009768
170	108475_at	0.000943	336.77	575.87	---	AI852851	XM_136178
171	109415_at	0.000945	779.53	1221	Hook1	AI646948	NM_030014
172	137185_i_at	0.000957	1184.1	1918.47	---	AI840674	---
173	97932_f_at	0.000966	570.9	714.9	Cd151	D89290	NM_009842
174	96236_at	0.000979	406.53	689.43	Cdc16	AW122965	NM_027276
175	115360_at	0.000988	1432.43	1783.27	Cul3	AI839569	NM_016716
176	164885_f_at	0.000989	427.03	835.33	---	AV335220	NM_009142
177	166582_i_at	0.000992	5648.53	6487.73	---	AV380822	---
178	98472_at	0.001008	103.17	153.67	---	Y00629	NM_010398
179	95053_s_at	0.00102	2661.73	3917.9	Sdhb	AA674669	NM_023374
180	99607_at	0.001022	2210.57	3859	Skp1a	Z47088	NM_011543
181	164502_r_at	0.001032	1298.77	2266.73	---	AV314810	NM_025594
182	115765_at	0.00104	815.97	1114.77	Shprh	AI849646	NM_172937
183	168820_at	0.00104	233.4	360.4	---	AV296698	---
184	93094_at	0.001087	109.83	203.83	Cdr2	U88588	NM_007672

Table 4

185	97448_at	0.001099	1841.57	2968.57	---	AI845165	NM_001004146 /// NM_177298
186	117188_at	0.001113	196	339.77	Esrrbl1	AW121981	NM_028680
187	96192_at	0.001117	626.13	839.37	Sp3	AF062567	NM_001018042 /// NM_011450
188	94042_f_at	0.00113	2643.43	3445.73	Gng5	AI843937	NM_010318
189	162049_f_at	0.001138	123.37	183.83	---	AV379304	NM_201352
190	160271_at	0.001139	737.23	920.83	---	AW121255	NM_027855 /// NM_212470
191	100095_at	0.001157	542.07	691.5	Scarb1	U37799	NM_016741
192	161715_f_at	0.00117	318.73	464.37	---	AV250651	NM_025667
193	116938_at	0.001173	2548.83	8227.57	Spry2	AI848233	NM_011897
194	112363_at	0.001178	1698.8	2587.3	Sorl1	AW048194	NM_011436
195	160431_at	0.001186	417.23	868.7	Mrpl12	AW124432	NM_027204
196	163581_at	0.001197	2913.23	4179.13	Dcamkl1	AI847732	NM_019978
197	102036_at	0.001207	297.23	421.8	1810004B07Rik	AW046757	NM_026909
198	104007_at	0.001213	220.83	374.73	Slc25a15	AA986782	NM_011017 /// NM_181325
199	100952_at	0.001217	629.97	856.57	Stim1	U47323	NM_009287
200	113541_at	0.001228	511.47	1015.3	2610019N13Rik	AI843578	NM_026989
201	98938_at	0.001234	498.27	602.5	1500026D16Rik	AI852184	NM_026616
202	106245_at	0.001234	1719.7	2170.67	Mllt6	AW048315	NM_139311
203	163946_at	0.001239	1441.03	2314.43	Baalc	AI591547	NM_080640
204	95749_at	0.001253	557.67	747.57	Armet	AW122364	NM_029103
205	93656_g_at	0.001264	405.43	593.03	Usf1	X95316	NM_009480
206	114562_at	0.001265	183.03	286	6430526J12Rik	AA710515	NM_172668
207	164006_at	0.001267	1066.5	1679	Slc7a4	AI853530	NM_144852
208	108905_at	0.00127	343.47	460.93	---	AI561437	NM_053193
209	101393_at	0.001273	62.93	137.77	Anxa3	AJ001633	NM_013470
210	170411_at	0.001273	814.07	1184.4	---	AV333428	NM_033574 /// NM_033575 /// NM_033576 /// NM_033577 /// NM_033578 /// NM_033579 /// NM_033580 /// NM_033581 /// NM_033582 /// NM_033583 /// NM_033584 /// NM_033585 /// NM_033586 /// NM_033587 /// NM_033588 /// NM_033589 /// NM_033590 /// NM_033591 /// NM_033592 /// NM_033593 /// NM_033594 /// NM_033595
211	116094_at	0.00128	967.1	1309.13	BC033915	AI846254	NM_027498
212	103524_at	0.00129	239.6	362	Cdan1	AA691078	XM_485054
213	107876_at	0.001298	4100.53	5696.23	2610017I09Rik	AW047950	NM_183252
214	114937_at	0.001303	1230.17	2087.53	BC032203	AI256570	XM_140041
215	107124_at	0.001315	541.23	834.77	2810021O14Rik	AI848296	NM_025480
216	95437_at	0.00132	396.73	522.07	---	AI836139	NM_011931
217	108440_at	0.001323	409.73	632.73	3100002B05Rik	AA832882	NM_026664
218	97204_s_at	0.001333	175.83	362.53	Dnajd1	AI850983	NM_025384
219	97770_s_at	0.001333	767.23	1112.33	D6Wsu176e	AA733372	NM_138587
220	100446_r_at	0.001339	6210.67	12236.33	Sprr1b	X91825	NM_009265

Table 4

221	94767_at	0.001339	5897.67	9771.8	Rpsl1	U93864	NM_013725
222	162442_r_at	0.001345	255.37	366	---	AV349550	---
223	163513_f_at	0.001351	259	616.27	Tm9sf2	AV232877	NM_080556
224	164317_f_at	0.001356	746.03	1241.27	---	AV232343	NM_145475
225	111352_at	0.001361	448.13	575.7	Snrpf	AW215724	---
226	115414_at	0.001388	753.9	985.3	AW545589	AI849017	NM_019805
227	100533_s_at	0.001396	116.4	166.9	Crem	M60285	NM_013498
228	130491_at	0.001417	3214.17	4305.13	Amn	AI853281	NM_033603
229	94302_at	0.001423	1013.27	1664.4	Psmd4	AF013099	NM_008951
230	97366_at	0.001429	565.93	734.63	BC026588	AI851024	NM_146075
231	112886_f_at	0.001442	325.13	518.93	AA517739	AA968017	XM_489602 /// XM_622764
232	165458_r_at	0.001445	1828.7	3048.5	2610020H08Rik	AV214281	NM_001004187 /// NM_028129
233	99535_at	0.001447	1197.17	1746.5	Ccrn4l	AW047630	NM_009834
234	161889_f_at	0.00146	5298.7	6223.67	---	AV102160	---
235	115150_at	0.00146	234.33	415.23	---	AI846687	NM_024479
236	163370_at	0.001462	334.5	671.93	Osbpl3	AI591488	NM_027881
237	167197_s_at	0.001469	746.93	1120.87	Sftpa	AV025377	NM_023134
238	135355_at	0.001473	2189.87	7430.73	---	AW228646	---
239	137241_f_at	0.001476	988.57	1528.23	---	AI835499	NM_007917
240	99185_at	0.001485	495.93	808.4	2810443J12Rik	AW047026	---
241	94194_s_at	0.00149	633.43	1178.5	Hcn2	AJ225122	NM_008226
242	170384_r_at	0.001492	663.93	1256.57	---	AV325109	NM_138744
243	110343_f_at	0.001493	379.87	630.67	Tubgcp5	AI448463	NM_146190
244	160395_at	0.001495	191.2	429.8	D11Ertd603e	AW046672	NM_026023
245	104778_at	0.001501	363.13	619.57	4933426E21Rik	AI503093	NM_001029912
246	107298_at	0.001509	2268.77	3566	---	AW050310	XM_489103
247	101989_at	0.001528	3640.67	4891.23	Uqcrc1	AW125380	NM_025407
248	162833_at	0.001543	1504.1	3256.33	4833436C18Rik	AI849772	XM_131380
249	106659_at	0.001552	299.5	480.2	6720484B16	AI851954	NM_172502
250	113524_at	0.001552	325.33	649.07	Pdhx	AI747428	NM_175094
251	101063_at	0.001555	238.33	742.23	Tncc	M29793	NM_009393
252	113656_at	0.001555	437.83	593.3	1110012M11Rik	AW050247	NM_028617
253	99656_at	0.001566	497.87	740.63	D8Ertd812e	AI849027	NM_198020
254	93531_at	0.00157	1653.57	2121.43	Ndufa8	AI853855	NM_026703
255	164659_f_at	0.001581	619.03	839.57	---	AV356562	---
256	166258_at	0.001592	3038.4	3743.23	Dact2	AW208410	NM_172826
257	AFFX-MUR_b2_at	0.001611	2802.8	3968.13	---	X63136	---
258	160742_at	0.001623	355.63	446.33	Plod3	AI840146	NM_011962

Table 4

259	95290_at	0.001645	337.43	611.2	Crhr1	X72305	NM_007762
260	103397_at	0.00165	359.23	508.97	Hrb	AA795486	NM_010472
261	111118_at	0.001654	118.2	175.4	Stk381	AI182733	NM_172734
262	103098_at	0.001656	789.17	967.17	Baiap2	AW045765	NM_130862
263	95161_at	0.001658	837.13	1257.27	Ctdsp2	AW120628	NM_146012
264	169823_at	0.001663	3036.43	3693.9	---	AV147884	---
265	93043_at	0.00168	4224.17	4990.97	Sdfr1	D50463	NM_009145
266	99106_at	0.001687	1771.4	3023.73	Cops6	AF071315	NM_012002
267	163093_at	0.001705	2449.5	4626.23	Mcoln1	AI841374	NM_053177
268	109807_f_at	0.001706	190.77	334.23	---	AI117666	---
269	163952_at	0.001707	608.13	745.33	Mov10l1	AA764119	NM_027905 /// XM_620496
270	134749_f_at	0.001712	2859.23	3607.7	---	AI662731	XM_620293
271	114904_at	0.001721	289.93	615.9	C730036H08	AI853072	NM_172928
272	164749_f_at	0.001722	1732.63	3755.23	---	AV154443	---
273	94562_at	0.001726	283.9	432.77	Gnpat	AI843968	NM_010322
274	108969_at	0.001738	531.2	754.87	Msi1h	AA220091	NM_008629
275	114332_at	0.001741	337.23	475.83	Btbd7	AI644118	NM_172806
276	139527_at	0.001744	2611.9	3571.47	4930471K13Rik	AW049290	NM_181074
277	113648_at	0.001756	2218.63	3036.53	2810437L13Rik	AW049458	NM_197980
278	107483_at	0.001774	355.67	561.2	---	AW050172	NM_001013753
279	163611_f_at	0.001777	1141.27	2395.1	Nudt11	AI843187	NM_021431
280	163409_at	0.001796	239.4	619.4	6330505F04Rik	AI627048	NM_172779
281	98904_at	0.001801	371.1	587.7	Mrpl35	AW061339	NM_025430
282	137542_at	0.001813	801.27	1640.5	AA881470	AI550484	NM_172724 /// NM_181066
283	135210_at	0.001833	860.2	1611.37	Polg	AI503064	NM_145946
284	104033_at	0.00186	644.97	849.33	Mgea6	AI841996	NM_146034
285	93119_at	0.001871	3831.3	6057.97	Cox5b	X53157	NM_009942
286	109418_at	0.001872	706.97	1184.93	A530089I17Rik	AI846894	NM_133999
287	162529_at	0.001874	3674.8	5195.93	Ndufs7	AI837272	NM_029272
288	97812_at	0.001876	443.3	715.7	Ranbp9	AF006465	NM_019930
289	98800_at	0.001894	252.93	435.47	Slc23a3	U25739	NM_194333
290	105496_at	0.001894	236.73	582.3	Hsf2	AA832774	NM_008297
291	93582_at	0.0019	274.87	329.57	Coq7	AF080580	NM_009940
292	137242_f_at	0.0019	2141.53	4183.57	---	AI836689	NM_021273
293	110969_at	0.00191	513.27	832.33	3110031B13Rik	AW123355	NM_026075
294	93410_at	0.001914	765.13	1055.2	1810073P09Rik	AW120840	XM_127323
295	103780_at	0.001928	110.7	194.73	1700021F05Rik	AW049510	NM_026411
296	93076_at	0.001932	2187.9	3001.9	Csnk1a1	AW124171	NM_146087

Table 4

297	160832_at	0.001946	348.6	410.23	Ldlr	Z19521	NM_010700
298	162806_at	0.001946	2818.2	4602.03	2410004H02Rik	AI154996	NM_145954
299	95565_at	0.001951	357.8	515.33	Mad2l1bp	AI852873	NM_025649
300	106469_at	0.001961	631.77	1705.77	Rtn4	AI835918	NM_024226 /// NM_194051 /// NM_194052 /// NM_194053 /// NM_194054
301	108515_at	0.001963	533.17	780.77	Tpcn1	AA866771	NM_145853
302	163658_at	0.00198	600.87	669.47	6430704M03Rik	AI851180	XM_131434
303	103420_at	0.001989	800.57	1031.17	Emd	U79753	NM_007927
304	100527_at	0.002003	1567.77	2088.93	D11Ertd99e	AW124744	NM_026618
305	113626_at	0.00202	345.27	531.7	3110031B13Rik	AW050102	NM_026075
306	100068_at	0.002041	973.33	1292.47	Aldh1a1	M74570	NM_013467
307	94259_at	0.002048	789.43	1316.63	5730442A20Rik	AB024935	NM_019766
308	164923_f_at	0.002048	359.2	538.07	---	AV091954	NM_026610
309	100903_at	0.002049	365.73	513.63	Adprtl2	AJ007780	NM_009632
310	166739_r_at	0.00205	3632.3	4280.57	---	AV331146	NM_145473
311	99184_at	0.002054	333.87	443.2	Csad	AW120896	NM_144942
312	96212_at	0.002063	1209.27	1662.3	2310061I04Rik	AI853918	XM_128627
313	112740_at	0.002076	564.53	1163.37	Thrap2	AA792120	NM_172424
314	95707_at	0.00208	1030.1	1793.7	2900010M23Rik	AA615853	NM_026063
315	113310_f_at	0.002085	2839.77	3625.27	Mjd	AA175228	---
316	100828_at	0.002086	509.2	656.7	---	AI648850	NM_010858
317	109416_at	0.002088	361.93	645.6	Pdgfa	AI835646	NM_008808
318	95529_at	0.002093	484.97	884.47	Dbnl	U58884	NM_013810
319	96652_at	0.002096	868	1142	Mrpl28	AI849911	NM_024227
320	111038_at	0.002113	1566.8	2485.3	Clasp2	AW047327	NM_029633
321	104651_at	0.002125	442.9	691.63	C330035N22Rik	AI839611	NM_172926
322	161127_i_at	0.002125	327.33	495.13	Rpl24	AV294412	NM_024218 /// XM_194389
323	170932_at	0.00213	1413.43	1854.67	---	AV102105	NM_133964
324	100534_at	0.002153	2422.17	2889.43	Tsnax	AI183109	NM_016909
325	97929_r_at	0.002155	385.3	525.43	Psmd9	AW124782	NM_026000
326	161763_r_at	0.002155	442.87	1719.63	Pip5k2c	AV303514	NM_054097
327	167926_f_at	0.002184	680.93	992.07	---	AV255693	NM_013830
328	95442_at	0.002205	1198	1512.2	MGC18837	AI835706	NM_178577
329	98132_at	0.002211	505.13	825.77	---	X01756	NM_007808
330	164491_at	0.002214	75.23	162.5	---	AV263513	---
331	95696_at	0.002221	1354.7	2447.6	Txnl2	AI840882	NM_023140
332	93379_at	0.002227	571.03	759.1	Dpysl4	Y09079	NM_011993

Table 4

333	116074_at	0.002256	1697.63	2450.23	Pvrl1	AI835281	NM_021424
334	115735_r_at	0.002276	739.93	1248.97	C6	AI326046	NM_016704
335	166381_f_at	0.002284	128.7	237.03	4931417E11Rik	AV278586	NM_025737
336	94246_at	0.002285	444.47	609.8	Ets2	J04103	NM_011809
337	92191_at	0.002292	150.57	234.33	2810410A08Rik	AI255450	XM_130324
338	96943_at	0.002293	1986.4	3339.73	---	AW125234	NM_145370
339	104861_at	0.002298	180.17	380.8	A530037C04Rik	AI552305	XM_283647
340	140436_at	0.002305	4315.2	5663.77	Mapk4	AW060644	NM_172632
341	116858_at	0.002312	709.77	954.6	Mafb	AI849704	NM_001004164
342	107028_s_at	0.002328	542.43	1026.07	5830445C04Rik	AW049312	NM_026366
343	96232_at	0.00233	632	1040.6	Cul2	AI854281	NM_029402
344	162962_at	0.002355	906.07	1372.97	B630019K06Rik	AI843180	NM_175327
345	164458_f_at	0.002356	457	840.67	---	AV150246	NM_025635
346	162094_f_at	0.002361	154.53	242.07	---	AV339425	NM_175394
347	111464_at	0.002364	887.93	1218.13	2410153K17Rik	AI840632	XM_486122
348	112307_at	0.002366	897.7	1069.9	AW541238	AI851057	XM_130491
349	112388_at	0.002372	2933.57	5959.2	Mmd	AW123069	NM_026178
350	113255_at	0.002372	57.33	103.47	C6.1A	AI844475	NM_145956
351	166313_r_at	0.002374	4058.83	5936.87	Stch	AV345032	NM_030201
352	96258_at	0.002375	2020.57	4019.6	Mgst3	AI843448	NM_025569
353	101093_at	0.002376	369.07	906.67	Col4a1	M15832	NM_009931
354	103695_f_at	0.002387	2023.33	2764.53	C330007P06Rik	AW047329	---
355	116927_at	0.002398	608.17	1256.37	Srebf1	AI848903	NM_009021
356	106620_at	0.002402	1128.13	1503.07	1500019J17Rik	AW120962	NM_026398
357	107154_f_at	0.002412	948.03	1406.23	---	AW215571	---
358	111849_at	0.002414	1760.87	2259.77	---	AW050288	NM_025808
359	168292_i_at	0.00243	3891.57	5698.53	---	AV304486	NM_145376
360	116312_at	0.002448	188.67	388.17	LOC234344	AW214291	XM_134209
361	113691_at	0.002449	527.43	749	Prkab2	AW049533	NM_182997
362	94002_at	0.002454	1159	1319.47	Cul1	AI849838	NM_012042
363	94807_at	0.002465	908.33	1205	Slc25a1	AI848354	NM_153150
364	137328_at	0.002467	2598.1	4366.53	---	AW060579	NM_011611 /// NM_170701 /// NM_170702 /// NM_170703 /// NM_170704
365	111837_at	0.002475	251.03	473.4	E430007K15Rik	AI854171	NM_145832 /// NM_211358
366	170227_at	0.00248	342.8	906.53	---	AV340157	---
367	162457_f_at	0.002498	3113.5	7294.6	---	AV003378	NM_008218
368	164560_at	0.002499	258.77	406	---	AV352226	---

Table 4

369	116189_at	0.002509	275.4	395.13	2810409H07Rik	AA120487	NM_025942 /// NM_030091
370	160482_at	0.00252	652.3	1181.6	Acaa1	AI841705	NM_130864
371	161879_r_at	0.002533	1064.33	1535.27	---	AV366282	NM_146012
372	106637_r_at	0.002539	1547.53	1827.67	1810013B01Rik	AI647933	NM_029631
373	106629_at	0.002541	253.5	370.07	4632411B12Rik	AI838125	NM_172652
374	95010_at	0.002548	589.93	888.47	Traf3	U21050	NM_011632
375	116137_at	0.002548	1853.83	2780.53	---	AI839836	NM_172884
376	96518_at	0.002559	177.47	302.93	BC037006	AU017197	XM_109956
377	104120_at	0.002571	709.73	1099.83	5330431N19Rik	AW049205	NM_172639
378	163241_at	0.002573	236.6	331.93	Bbs4	AW045807	NM_175325
379	93102_f_at	0.002574	512.97	799.9	Actg2	U20365	NM_009610
380	109363_at	0.002576	1764.33	2606.4	Adar	AI847526	NM_019655
381	101787_f_at	0.002589	1369.57	1818.23	---	X16672	NM_009834 /// XM_484417 /// XM_484511 /// XM_485016 /// XM_485943 /// XM_486935 /// XM_489830 /// XM_619223 /// XM_620378 /// XM_622930
382	160230_at	0.002593	1841.33	2394.6	---	AI852363	---
383	92394_f_at	0.002594	274.6	489.8	Crebl1	AB010266	NM_017406
384	162481_f_at	0.002603	835.9	1032.2	---	AV105090	NM_177231 /// NM_178220
385	160840_at	0.002604	222.37	346.33	Arhgef3	AI853706	NM_027871
386	101406_at	0.002611	151.67	222.43	Sult2b1	AF026072	NM_017465
387	161644_f_at	0.002637	709.23	980.43	---	AV080704	NM_010255
388	161436_s_at	0.002638	1017	1412.47	---	AV345565	NM_001024837 /// NM_001024838 /// NM_001024839 /// NM_001024840 /// NM_130895
389	96858_at	0.002653	595.57	1072.6	Pdcd8	AF100927	NM_012019
390	96873_at	0.002669	570.87	767.3	AI591476	AI843287	NM_025816
391	101079_at	0.002692	223.3	311.1	Nxf1	AF093140	NM_016813
392	99669_at	0.002734	398.97	558.47	Lgals1	X15986	NM_008495
393	98937_at	0.002737	847.27	1032.37	Tbrg1	AW049795	NM_025289
394	117217_at	0.002749	1057.33	2014.1	Wasf1	AI838537	NM_031877
395	101596_at	0.002755	109.83	212.5	---	C78859	---
396	104117_at	0.002771	95.9	164.33	4930421J07Rik	AI836641	NM_027149
397	104562_at	0.002784	313.93	383.9	5730403M16Rik	AW049632	NM_172738
398	112003_at	0.00279	1054.73	1686.87	B430110G05Rik	AW122074	NM_178696
399	101067_at	0.002794	697.5	840	BC023814	AW124711	NM_026591
400	94132_at	0.00281	757.33	933.87	---	X03920	NM_008160
401	165671_f_at	0.002811	620.3	918.67	Fn3k	AI852365	NM_022014
402	102308_at	0.002814	395.03	699.3	Tulp3	AF045582	NM_011657
403	96621_at	0.002815	444.13	664.33	1110061L23Rik	AW048608	NM_029406
404	161487_f_at	0.002853	612.27	891.77	---	AV080542	---

Table 4

405	116103_at	0.002862	1239.6	1631.4	---	AW121390	---
406	101486_at	0.002868	1160.53	1777.63	Psmb10	Y10875	NM_013640
407	94830_at	0.002886	576.9	906.7	BC005537	AI854300	NM_024473
408	161495_r_at	0.002889	136.73	193.2	---	AV091448	NM_009897
409	103371_at	0.002898	1203.1	1593.7	---	AF100956	NM_008202
410	97374_at	0.002911	319.77	576.63	2810025M15Rik	AI840458	NM_027274
411	167190_r_at	0.002918	1009.07	1861.67	---	AI448406	XM_137762
412	104954_at	0.002922	339.87	540.83	---	AI508971	---
413	169799_r_at	0.002946	1089.77	1568.47	---	AV124293	NM_020560
414	116178_at	0.002952	515.67	721.3	Hmga2	AA980725	---
415	95602_at	0.002976	2253.13	2837.9	Trpc4ap	AI848135	NM_019828
416	93511_at	0.00298	390.23	660.9	Itm2a	L38971	NM_008409
417	115190_at	0.003001	332.3	499.67	Piasy	AA671180	NM_021501
418	95493_at	0.003023	658.47	876.17	Col6a1	X66405	NM_009933
419	113730_at	0.003034	458.8	725.33	Esrrbl1	AA920235	NM_028680
420	93257_at	0.00305	861.4	1083.17	Ddx1	AW048287	NM_134040
421	103584_at	0.003055	4659.17	6615.87	4933407C03Rik	AW124334	---
422	166464_r_at	0.003064	204.1	392.73	---	AV309629	NM_145928
423	109705_s_at	0.003066	1611.2	2272.17	D2Bwg1335e	AW120924	XM_484981
424	94530_at	0.003071	501.67	628.8	C85417	AI840376	NM_145445
425	165367_f_at	0.003072	2382.5	3381.1	---	AV018700	---
426	99339_r_at	0.003094	491.7	1041.53	Kcnd2	AI839615	NM_019697
427	99947_at	0.003096	260	332	Tial1	U55861	NM_009383
428	104371_at	0.003097	195.7	294.47	Dgat1	AF078752	NM_010046
429	94113_at	0.003097	258.43	461.87	---	AA163908	---
430	163126_at	0.0031	274.9	511.6	Rbm16	AI480847	XM_619423
431	162524_at	0.003101	2273.53	2987.37	E230019G03Rik	AW122308	NM_053178
432	103527_at	0.003106	341.87	452.93	A330108F03Rik	AW124360	NM_153142
433	98862_at	0.003117	235.57	364.37	Wnt10a	U61969	NM_009518
434	170223_f_at	0.003136	6570.87	9056.2	---	AV064603	NM_080559
435	112975_at	0.003163	374.7	579.2	A330074B06Rik	AI195532	---
436	104071_at	0.003169	2434.1	2853.23	Tnpo2	AI852433	NM_145390
437	163638_i_at	0.003173	92.43	154.3	4933403G14Rik	AI835009	NM_028908
438	114497_at	0.003185	1905.83	2329.03	1110012J17Rik	AW120806	NM_172963
439	107572_at	0.003201	1258.63	1507.6	Taz	AW046145	NM_181516
440	105746_at	0.003227	1847.8	2558.3	---	AW121141	---
441	107319_at	0.003238	212.57	359.4	---	AW049191	XM_358254
442	98575_at	0.003248	990.23	1293.23	Fasn	X13135	NM_007988

Table 4

443	98072_r_at	0.003266	35.63	83.47	Dck	X77731	NM_007832
444	110545_at	0.003283	209.97	409.97	---	AI593064	NM_029770
445	106872_at	0.003284	1166.07	1426.97	AW046396	AW046396	NM_177836
446	104299_at	0.0033	414.13	564.37	Zdhhc14	AI842472	NM_146073
447	101179_at	0.003313	1433.17	2331.53	---	D50494	---
448	97207_f_at	0.00333	269.87	495.17	Lypla1	AI875934	NM_008866
449	117321_at	0.003333	1865.8	2393.9	---	AI854488	NM_027086
450	103748_at	0.003336	443.4	1198.1	4933407C03Rik	AW125627	---
451	100915_at	0.003345	460.1	966.33	Myh9	AW125698	NM_022410 /// NM_181327
452	164530_f_at	0.003358	1226.27	1605	---	AV350292	NM_198326 /// XM_485605
453	102431_at	0.003361	5696.77	9021	Mapt	M18775	NM_010838
454	96076_at	0.003371	588.8	868.27	Stx5a	AW121716	NM_019829
455	100718_at	0.003375	1836.57	3298.83	Ptma	X56135	NM_008972
456	164407_f_at	0.003391	1218.87	1886.3	---	AV344241	NM_019705
457	160869_at	0.003416	532	718.2	Sirt3	AI849490	NM_022433
458	164680_s_at	0.003418	727.6	1115.23	---	AV312895	NM_198163
459	93033_at	0.003423	115.6	207.53	Ube2e3	X92664	NM_009454
460	96875_r_at	0.00343	49.6	126.67	AI591476	AI841410	NM_025816
461	115631_at	0.00343	726.03	1034.37	---	AI450274	XM_128587
462	112361_at	0.003434	1090.63	1411.63	Coq6	AW124800	NM_172582
463	105343_at	0.003447	244.37	481.7	---	AI156452	---
464	99620_at	0.003457	75	148.77	Sfpq	AW060546	NM_023603
465	163663_at	0.003471	1046.6	1711.47	---	AI846080	NM_017377
466	111845_at	0.003472	3064.13	5557.53	---	AW049453	---
467	164112_at	0.003479	540.47	913.9	4632415L05Rik	AI662792	---
468	160146_r_at	0.003491	381.23	531.33	Polr2c	D83999	NM_009090
469	102108_f_at	0.003505	203.9	284.37	---	AI505453	NM_022410 /// NM_181327
470	162573_at	0.003514	2720.87	3517.13	5330410G16Rik	AW045610	NM_182991
471	164266_at	0.003514	270.8	517.7	Nlk	AV330397	NM_008702
472	107462_at	0.003527	429.77	639	5730528L13Rik	AW047417	NM_028137
473	109630_at	0.003531	184.73	306.8	C630007L23Rik	AA790799	XM_283496
474	112876_at	0.003536	5634.33	7633.17	---	AA920095	NM_001024474 /// XM_619099
475	111970_at	0.003539	122.8	285.6	---	AI616223	XM_127961
476	116877_at	0.003553	4406.53	5481.6	---	AW060474	---
477	168591_r_at	0.003555	1184.1	1912.2	---	AV210831	---
478	104242_f_at	0.003569	512.67	642.57	4930578F06Rik	AI835622	NM_029545
479	170586_r_at	0.003582	12780.5	14950.93	---	AV258212	XM_354949
480	97443_at	0.003583	1321.53	1860.07	Mrpl52	AI850850	NM_026851

Table 4

481	160075_at	0.003588	281.1	410.17	Nit1	AF069988	NM_012049
482	93829_at	0.003591	164.33	222.4	Rod1	AW107884	NM_144904 /// NM_178164
483	93421_at	0.003608	1618.93	2030.2	Pftk1	AF033655	NM_011074
484	135202_at	0.003613	3308.1	4120.73	---	AA420310	---
485	109734_at	0.003614	2051.73	2919.77	Dnclic1	AI847889	NM_146229
486	164532_r_at	0.003628	1082.03	1710.4	---	AV350579	NM_145401
487	98032_at	0.003634	222.83	346.43	Zfp35	M36146	NM_011755
488	162733_at	0.003643	723.6	960.63	Ptpla	AA870639	NM_001012396 /// NM_013935
489	110157_at	0.003679	1265.8	1909	BC024814	AW124961	NM_146247
490	110435_at	0.003701	190.4	307.7	AI316828	AI851412	NR_002321 /// NR_002322
491	115608_at	0.003733	112.97	395.97	---	AI639736	NM_011861 /// NM_178365
492	160090_f_at	0.003754	12457.6	14228.17	Aldo1	Y00516	NM_007438
493	92842_r_at	0.003768	29.03	48.7	Chgb	X51429	NM_007694
494	114058_at	0.003789	257.8	376.47	3000004C01Rik	AA152809	NM_197959
495	137531_at	0.003793	3739.7	5324.67	---	AI661034	---
496	95147_at	0.003865	620.37	745.73	Pgls	AI843795	NM_025396
497	112310_r_at	0.003866	85.63	170.07	Slc25a16	AI852842	NM_175194
498	110279_at	0.003874	2408.4	2561.97	Tmc4	AW122421	NM_029934
499	115669_at	0.003881	266.93	395.47	A830039N02Rik	AW125656	NM_028894
500	167951_at	0.003901	1346.63	1774.1	---	AV234690	---
501	95091_at	0.003905	741.33	930.33	Sec13r	AI839895	NM_024206
502	95453_f_at	0.003911	783.13	1034.93	S100a1	AF087687	NM_011309
503	117294_at	0.003927	8450.23	10520	Zfp179	AI838352	NM_009548
504	98953_at	0.003934	2833	4231.4	1500010M16Rik	AW048032	NM_026892
505	95655_at	0.003936	37.33	64.3	5830411E10Rik	AA717740	NM_028696
506	100429_at	0.003943	134.8	234.47	---	U89155	NM_008911
507	92628_at	0.00395	2040.6	2942	Rpl36	X75895	NM_018730
508	130534_i_at	0.003982	23275.6	28562.33	4930471K13Rik	AW123836	NM_181074
509	109788_f_at	0.003992	537.9	915.47	---	AI481314	NM_172965
510	99335_at	0.004026	1556.93	3263.03	Hk1	J05277	NM_010438
511	109797_at	0.004055	959.7	1198.7	Zfp60	AI893630	NM_009560
512	160121_at	0.004078	315.63	412.57	Galk2	AW125050	NM_175154
513	97201_s_at	0.00409	2987.17	4563.83	Ndufa5	AA823381	NM_026614
514	101210_at	0.004102	745.33	1032.63	---	R74626	XM_620798
515	92424_at	0.004119	168.93	288.67	AI839920	AI843426	NM_182996
516	165022_f_at	0.004141	463.73	834.4	---	AV358934	NM_029814
517	115968_at	0.004144	187.8	278.43	5033405K12Rik	AI563646	NM_153567
518	135781_at	0.004146	932.7	1267.73	---	AI893789	---

Table 4

519	109715_at	0.004153	4005.7	4946.97	Cugbp1	AW046738	NM_017368 /// NM_198683
520	97356_at	0.004214	1687.1	2539.17	1810008O21Rik	AI839653	NM_026938
521	97273_at	0.004227	610.63	752.4	Ars2	AI845953	NM_031405
522	92555_at	0.004249	199.5	295.7	Tm4sf6	AF053454	NM_019656
523	106911_at	0.004271	666.93	1027.8	Dnm	AW121763	NM_010065
524	116577_at	0.004281	456.1	639.63	C230080I20Rik	AI450355	XM_485838
525	96021_at	0.004297	791.6	994.03	0710001C05Rik	AI854264	XM_203592
526	104106_at	0.0043	173	291.07	Sbno1	AI837830	XM_355637
527	104716_at	0.004306	136.53	180.77	Rbp1	X60367	NM_011254
528	170945_f_at	0.004312	1386.03	1623.37	---	AV112101	NM_011573
529	164746_f_at	0.004314	1786.03	3372.7	---	AV147912	---
530	130033_at	0.004346	274.73	367.93	1810012P15Rik	AI593446	XM_358407
531	160964_at	0.004351	3197.3	3936.8	D16Bwg1494e	AI838494	XM_358773 /// XM_622611
532	164636_f_at	0.004356	118.9	217.4	---	AV229875	NM_144806 /// XM_130282
533	169766_r_at	0.004387	791.37	1128.17	---	AV101347	NM_026797
534	135613_at	0.004389	198.87	650.13	Trim41	AI505867	XM_618865
535	96291_f_at	0.004407	2425.8	3064.27	---	AI835847	NM_010888
536	113200_at	0.004409	1147.3	1507.4	---	AW122883	NM_133700
537	112719_at	0.00441	1932.7	3386.8	D6Ertd349e	AW215036	NM_182784
538	94835_f_at	0.004433	13640.1	16905.53	Tubb2	M28739	NM_009450
539	164377_f_at	0.004443	2840.03	3954.67	---	AV322737	NM_001013256 /// NM_026889
540	164725_f_at	0.004451	86.83	238.37	---	AV083420	---
541	164305_at	0.004453	93.47	237	---	AV237879	---
542	103875_at	0.004457	529.27	651.2	AW552001	AA967717	NM_031375
543	100515_at	0.004485	543.1	867.03	Furin	X54056	NM_011046
544	136224_at	0.004491	537.7	724.8	MGC39058	AI836305	NM_138949
545	164090_i_at	0.004511	117.33	276.4	---	AI462901	---
546	164301_f_at	0.004516	151.63	273.7	---	AV235519	NM_026501 /// NM_028933
547	101959_r_at	0.004537	777.2	1213.1	Tfdp1	X72310	NM_009361
548	169465_s_at	0.004537	1052.07	1840.7	---	AV156900	NM_028454
549	161808_f_at	0.004539	229.4	388.07	---	AV371846	NM_007965
550	100576_at	0.004561	219.23	309.87	Pafah1b3	U57746	NM_008776
551	115965_at	0.004586	1052.27	1364.13	---	AI851716	---
552	163920_at	0.004602	154.57	252.77	E330005K07Rik	AI592356	NM_027777
553	113145_at	0.00461	752.8	1021.1	Xpo5	AI838163	NM_028198
554	93559_at	0.004637	784.5	1034.2	Apex1	D90374	NM_009687
555	166527_f_at	0.004649	462.7	675.3	---	AV303385	NM_133248
556	161494_f_at	0.004658	395.9	580.27	---	AV090776	NM_025313

Table 4

557	111745_at	0.004667	263.43	346.93	Zfp148	AI225326	NM_011749
558	113588_f_at	0.004681	4234.97	5456.63	Kif5b	AI838375	NM_008448
559	109925_at	0.00469	547.03	1147.5	AI043120	AW123749	XM_128924
560	113312_at	0.004725	1272.43	1708.63	Pscd1	AI848583	NM_011180
561	164193_at	0.004733	221.53	319.03	3830421F13Rik	AA289928	NM_027226
562	104491_at	0.004753	233.13	337.1	1110054G21Rik	AI509330	NM_172992
563	140323_r_at	0.004762	1553.6	2452.43	1110019L22Rik	AA592566	NM_008688
564	95470_at	0.004765	364.73	702.5	Gdpd1	AI846025	NM_026550
565	93019_at	0.004793	733.3	1196.83	H2afx	Z35401	NM_010436
566	115334_at	0.004799	776.1	1155.23	---	AI449433	---
567	100122_at	0.004801	624.73	936	Gnb5	L34290	NM_010313 /// NM_138719
568	103345_at	0.004819	4014	4506.83	Spna2	AW046708	XM_207079 /// XM_622887
569	161816_r_at	0.004835	1729.7	2391.03	---	AV375661	NM_019821
570	93067_f_at	0.004842	281.53	451.8	Hist2h2aa1	U62674	NM_013549 /// NM_178212 /// XM_619173
571	100041_at	0.00485	967.97	1454.87	3010027G13Rik	AW124133	NM_026542
572	169499_r_at	0.004864	680.97	1453.13	---	AV209532	XM_130726
573	108536_at	0.004885	360.1	501.83	Slc15a4	AI850994	NM_133895
574	111882_r_at	0.004901	94.1	197.03	Tspyl	AI843800	NM_009433
575	110746_f_at	0.004902	1635.23	2584.83	---	AA760217	---
576	111355_at	0.00492	142.53	262.4	2010110K24Rik	AW123041	NM_025934
577	112291_r_at	0.004923	123	283.63	BC023823	AA655542	NM_153566
578	98418_at	0.004927	1675.27	2562.53	Dvl1	U10115	NM_010091
579	163058_at	0.004937	293.1	356.17	Sox9	AI852411	NM_011448
580	110165_at	0.004949	141.23	236.83	Nanos1	AW049758	NM_178421
581	108753_at	0.00496	731.37	913.47	1810027I20Rik	AW048441	NM_026950
582	102912_at	0.004961	2752.2	3279.67	5430432P15Rik	AI265115	XM_129246
583	108289_at	0.004976	213.43	325.83	BC031593	AI644063	NM_146063
584	136199_at	0.004983	1190.57	1684.47	---	AI853239	---
585	99096_at	0.004984	714.13	833.57	Ddx24	U46690	NM_020494
586	163190_at	0.004987	192.73	361.97	Acvrl1	AI115505	NM_009612
587	105469_at	0.004989	364.87	593.37	BC019560	AI642424	---
588	104366_at	0.005013	526.93	775.9	BC039093	AW047831	XM_131700
589	161510_f_at	0.005032	7592.1	10179.57	---	AV151915	NM_011322
590	160195_at	0.005033	1742.83	2244.5	1200013P24Rik	AI846961	NM_029090
591	113701_at	0.005063	1260.2	1962.37	Zdhhc8	AW045740	NM_172151
592	103779_at	0.005068	399.8	678.87	1810012I01Rik	AI852829	---
593	95023_at	0.005073	2218.87	2904.5	BC023957	AW050353	NM_172257
594	93118_at	0.005081	123.13	239.23	Hnrpa2b1	AI844131	NM_016806 /// NM_182650

Table 4

595	94929_at	0.005094	723.7	1177.63	Ptpn1	M97590	NM_011201
596	164717_f_at	0.005113	266.63	427.63	---	AV053535	---
597	106615_at	0.005114	1033.63	1447	Ankrd17	AW208385	NM_030886 /// NM_198010
598	163015_at	0.005122	838.77	1249.63	Amn	AA929443	NM_033603
599	169773_r_at	0.005123	2021.23	3037.5	---	AV102460	NM_010094
600	171283_r_at	0.005124	4466.87	6316.77	AV216498	---	
601	94062_at	0.005126	2633	3822.07	Ndufv2	AI847609	XM_128725
602	160170_at	0.005127	4356.4	5230	Stmn3	AF069708	NM_009133
603	107581_at	0.005134	2021.43	2974.73	Cdc42bpb	AI843686	NM_183016
604	165757_i_at	0.005137	2443.2	3305.23	---	AI844065	XM_620310
605	101499_at	0.005146	478.1	634.5	Ilk	U94479	NM_010562
606	160263_r_at	0.005161	391.5	552.6	Ndfip2	AI840981	NM_029561
607	94238_at	0.005163	35.43	104.4	2310046G15Rik	AW228316	NM_029614
608	115402_at	0.005166	699.7	915.97	2700087I09Rik	AW120513	NM_198161
609	107130_at	0.005171	149.03	188.4	4931428F02Rik	AW214372	NM_027642
610	AFFX-MUR_b2_at	0.005177	1440.33	2060.63	---	X63136	---
611	115129_at	0.005195	494.63	771.17	AW907654	AW123461	NM_199322
612	160661_at	0.005202	500.6	633.6	5730472N09Rik	AI840615	NM_175392
613	100628_at	0.005234	1079.7	2766.13	---	AI840263	NM_025523
614	109157_at	0.005246	277.37	438	Mrps30	AI847000	NM_021556
615	113618_r_at	0.005281	178.43	315	2810002N01Rik	AI663283	NM_027404
616	104725_at	0.005293	175.63	262.87	Arhq	AW060401	NM_145491
617	114752_at	0.005294	38.5	115.4	D930038M13Rik	AI843572	NM_001014399 /// NM_001014422 /// NM_001014423 /// NM_001014424 /// NM_178790
618	96296_at	0.0053	296.43	439.03	Mrpl15	AI843685	NM_025300
619	160801_at	0.005308	776.63	947.27	2310009N05Rik	AW061073	NM_025861
620	110763_at	0.00531	3386.87	4491.6	Hdac11	AI835406	NM_144919
621	104605_at	0.005329	577.43	739.57	1110001I14Rik	AW047554	NM_197985
622	94818_at	0.00534	600.33	798.93	Ogt	AW047223	NM_139144
623	112900_at	0.005343	1006.13	1554.6	Mrp63	AA682034	NM_026401
624	102137_f_at	0.005359	1423.37	1746.3	---	AI845856	---
625	111894_at	0.005369	448.23	688.53	Mrpl32	AA734460	NM_029271
626	98557_f_at	0.005373	3316.07	4184.43	Psmb4	U65636	NM_008945
627	137556_r_at	0.005373	818.17	1541.17	---	AI606152	---
628	165178_f_at	0.005381	478.17	649.97	---	AV378746	NM_011573
629	168187_at	0.005393	237.3	393.53	Smarca1	AV301607	NM_053123
630	138052_g_at	0.005404	3397.03	5305.33	---	AI836889	NM_201371
631	100964_at	0.005417	1625.2	2146.67	Vti1b	AF035208	NM_016800

Table 4

632	115251_at	0.005417	1177.47	1492.83	Katnb1	AA795006	NM_028805
633	93319_at	0.005421	396.47	602.23	Rasa3	U20238	NM_009025
634	162971_r_at	0.005424	134.03	224.1	C330023F11Rik	AW124862	NM_178653
635	104345_at	0.005471	427.53	561.63	Exo70	AF014461	NM_016857
636	98029_at	0.005483	369.6	531.23	3110056O03Rik	AW060459	NM_175195
637	165329_r_at	0.005485	1185.37	1881.23	---	AV313208	NM_019705
638	111966_at	0.005492	758.53	1374.5	Hist3h2ba	AI836766	NM_030082
639	98884_r_at	0.005501	414.7	751.6	Ndel1	AI837311	NM_023668
640	103732_at	0.005519	1159.83	1478.07	Pib5pa	AI850079	NM_172439
641	129210_at	0.005523	541.27	791.03	---	AI426417	---
642	105115_at	0.005536	509.6	706.9	C130058G22Rik	AI549929	XM_484360
643	160129_at	0.005546	698.3	840.93	Eef1d	AI839632	NM_023240 /// NM_029663
644	95131_f_at	0.005553	5167.67	6840.3	Ndufb2	AI852592	NM_026612
645	134206_f_at	0.005572	7032.1	8460.2	Grpel1	AI461632	XM_132031
646	164838_f_at	0.005599	122.67	285	---	AV342860	NM_027905
647	101081_at	0.005623	2832.8	3525.9	Ctbp1	AJ010483	NM_013502
648	164621_i_at	0.005626	4209.67	6580.93	---	AV157355	NM_053257 /// XM_484165 /// XM_486535
649	166118_i_at	0.005628	1599.1	2410.1	Rad51ap1	AV115378	NM_009013
650	162771_at	0.005645	1480.97	1814.4	0610007H07Rik	AW123990	NM_026617
651	112913_at	0.005648	489.93	931.33	mKIAA1064	AI836838	NM_198631
652	95081_at	0.00566	249.87	434.93	2310032N20Rik	AI840176	NM_027148
653	164461_f_at	0.005675	254.03	492.33	---	AV175309	NM_026130 /// XM_618904
654	101462_r_at	0.005678	122.67	324.97	Pja1	U06944	NM_008853
655	106638_at	0.005685	535.7	744.37	Ptgfrn	AA762192	NM_011197
656	164988_f_at	0.005685	1025.77	1673.7	---	AV369027	NM_027166
657	167794_f_at	0.005696	293.8	394.03	Stag3	AV274515	NM_016964
658	108614_f_at	0.005717	29193.9	32705.13	---	AI845104	NM_001018063 /// NM_024170 /// NM_028375
659	98525_f_at	0.005735	2463.07	3947.1	D14Wsu89e	AJ007909	NM_133362
660	165276_r_at	0.005742	464.87	1362.1	4733401O11Rik	AV151703	NM_172406
661	162600_at	0.005745	415.27	582.17	Tgfbr2	AI853795	NM_009371 /// NM_029575
662	93991_at	0.005752	6583.7	7901.33	Mor1	X07295	NM_008617
663	96289_at	0.005768	920.67	1226.37	Stoml2	AW061287	NM_023231
664	160805_s_at	0.005777	510.33	626.67	Mpdu1	AB025354	NM_011900
665	94047_at	0.005782	816.97	1185.7	0610031J06Rik	AW122935	NM_020003
666	114671_at	0.005796	439.8	570.2	2700082D03Rik	AI841352	NM_026031
667	102700_at	0.005804	3409.23	4645.33	Tbr1	U49251	NM_009322
668	95137_at	0.005805	566.57	749.37	1810014L12Rik	AI852985	NM_133706
669	100079_at	0.005807	2636.17	3370.53	Ndufb9	AI845556	NM_023172

Table 4

670	106572_at	0.005827	3035.8	4093	Mtmr6	AI847812	NM_144843
671	113331_at	0.005841	4354.27	5854.93	Wdr7	AI846569	XM_140391
672	100972_s_at	0.005843	2173.07	2862.8	Ccl27	AW124975	NM_011336
673	161183_at	0.005865	193.27	303.2	---	AV244370	NM_010017
674	162735_at	0.005871	300.43	437.83	Mknk1	AA655158	NM_021461
675	161363_r_at	0.005872	910.8	1417.93	---	AV217354	---
676	106274_at	0.005899	788.5	1013.83	2210412D01Rik	AI835482	NM_133722
677	103894_at	0.005925	861.47	1130.87	Shkbp1	AW060871	NM_138676
678	136270_at	0.005938	374.43	622.6	Crhbp	AI854101	NM_198408
679	116607_at	0.00594	153.5	351.63	9130001M19Rik	AA667097	NM_001007568
680	167764_f_at	0.00599	2368.87	4642.3	Laptm5	AV330551	NM_010686
681	101492_at	0.005999	409.23	584.43	Pin1	AW047032	NM_023371
682	111976_at	0.006026	301.37	486.37	---	AA960347	NM_025534
683	100101_at	0.006034	979.57	1243.67	Snrpa	L15447	NM_015782
684	111988_g_at	0.006086	690.03	793.07	Dhx8	AI550600	NM_144831
685	99651_at	0.006094	562.73	807.17	2610209M04Rik	AI849549	NM_025665
686	170031_f_at	0.006097	485.23	672.63	---	AV300000	NM_008872
687	111889_at	0.006102	324.27	514.4	Gtf3a	AA672564	NM_011669
688	135828_at	0.006108	824.8	1149.53	LOC329416	AA574572	NM_181547
689	114122_at	0.00614	1097.7	1256.83	Anks1	AW124232	NM_181413
690	162501_at	0.006156	163.43	328.43	---	AV172042	---
691	115559_at	0.006167	443.9	610.37	2900024C23Rik	AI852706	NM_026062
692	164443_at	0.006183	150.5	343.63	---	AV107881	NM_133668
693	92771_at	0.006215	507.8	728.77	Zfp207	AB013357	NM_011751
694	165372_at	0.006215	658.4	997.13	---	AV056802	NM_021386 /// NM_023878
695	163841_f_at	0.006242	580.57	813.2	BC031781	AI264993	NM_145943
696	162263_f_at	0.006271	159.4	236.97	---	AV357656	NM_008482
697	107612_at	0.006279	1505.13	1894.23	BC017607	AW121470	NM_144924
698	97254_at	0.006282	366.8	464.57	Rbm8	AA690061	NM_025875
699	113564_at	0.006292	719.73	1202.93	1810014F10Rik	AI837984	NM_026928
700	101002_at	0.006296	2398.37	2945.27	Oazin	AF032128	NM_018745
701	112967_at	0.006312	3438.87	5264.27	Ppp1r1c	AW050351	NM_028755 /// NM_033264
702	169033_r_at	0.006325	393.63	682.7	---	AV151387	NM_008786
703	102727_at	0.006326	700.13	2233.63	Bdnf	X55573	NM_007540
704	113299_at	0.006341	4085.73	5957.63	Tnnt1	AW123040	NM_172894
705	164550_f_at	0.006354	659.2	1025.63	---	AV299991	NM_001033573 /// NM_025883 /// XM_484749
706	97353_at	0.00636	755.1	938.3	Dab2ip	AI837497	NM_001001602

Table 4

707	129251_r_at	0.006363	305.9	410.13	2610511M17Rik	AW047226	---	
708	106597_at	0.006376	327.27	449.9	Gemin7	AW049569	NM_027189	
709	93390_g_at	0.006395	100.5	134.63	Prom1	AF039663	NM_008935	
710	138968_f_at	0.006396	3948	4482.63	Adcy5	AW121902	NM_001012765	
711	109817_f_at	0.00642	1368.9	1989.67	---	AI893828	NM_009941	
712	106502_at	0.006447	2331	3139.1	Rap2ip	AI844940	NM_016759	
713	94247_at	0.006448	65.83	164.57	5730453H04Rik	AA600542	XM_621314	
714	94826_at	0.00648	682.53	845.67	Itgb4bp	Y11460	NM_010579	
715	101568_at	0.006487	426	563.17	1700024N20Rik	AW227620	NM_054057	
716	93178_at	0.006516	5111.87	6742.97	Ngef	AW050346	NM_019867	
717	104578_f_at	0.006521	1082.57	1460.1	Strm	AI195392	NM_134156	
718	101854_r_at	0.006522	314.5	712.7	Bat3	AI844178	---	
719	165300_i_at	0.006523	409.17	682.53	---	AV240127	---	
720	110286_at	0.006524	426.9	522.9	Maob	AI194762	NM_172778	
721	105688_f_at	0.006539	2163.1	2981.6	---	AI842855	NM_177643	
722	96951_at	0.006572	4327.4	5086	Atp6v1d	AI839795	NM_023721	
723	160168_at	0.0066	562.43	676.5	Fbxo3	AW125686	NM_020593 /// NM_212433	
724	102268_at	0.006619	531.07	699.83	1700021P10Rik	AW123015	NM_025852 /// NM_178383	
725	165617_at	0.006628	616.73	907.8	Ptplb	AI608246	NM_023587	
726	109989_at	0.006675	310.57	518.2	BC003236	AW124029	NM_030249	
727	94979_at	0.006686	679.87	862.8	BC018507	AW121624	XM_358313	
728	95132_r_at	0.006697	3870.33	6418.43	Ndufb2	AI852592	NM_026612	
729	161948_f_at	0.006721	194.43	250.2	---	AV214912	---	
730	104115_at	0.006723	308.73	381.83	Psme4	AA867340	NM_134013	
731	113671_at	0.006729	136.57	254.4	Dpys	AI786732	NM_022722	
732	97917_at	0.006732	609.87	762.73	Gcn5l1	Y13778	NM_015740	
733	164847_f_at	0.006736	280.57	443.63	---	AV367709	NM_019956	
734	92528_at	0.006745	1234.63	2116.53	Bai1	AI851724	NM_174991	
735	103672_at	0.006749	377.47	493.47	---	AW122572	NM_030064	
736	108565_at	0.006754	767.57	1006.03	E430002G05Rik	AI853095	NM_173749	
737	95385_at	0.006771	526.63	629.83	AA408556	AI643119	NM_199447	
738	110750_at	0.006781	1052.4	1253.67	2410016O06Rik	AA756518	NM_023633	
739	164280_f_at	0.006785	382.23	771.67	---	AV160326	NM_080595	
740	130687_at	0.006786	2890.07	3786.07	---	AI851398	---	
741	160426_at	0.006787	573.1	667.6	Rpo1-1	D31966	NM_009085	
742	136291_at	0.006801	1107.23	1363.77	---	AI838424	---	
743	161221_f_at	0.006806	112.07	178.6	---	AV253908	NM_012055	
744	103935_at	0.006838	284.6	484.47	Atp2a3	AI504474	NM_016745	

Table 4

745	160350_at	0.006881	669.93	949.07	Gstz1	AW060750	NM_010363
746	103534_at	0.0069	7298.03	12812.07	---	V00722	NM_016956
747	107629_at	0.006956	1195.77	1684.57	2610010O19Rik	AW048768	NM_144528
748	94516_f_at	0.006961	1416.3	3474.57	Penk1	M55181	NM_001002927
749	107111_at	0.006966	1203.73	1555.57	1200013I08Rik	AI836558	NM_028774
750	164889_f_at	0.006979	160.47	345.27	---	AV337140	---
751	163590_at	0.006981	403.83	502.33	BC011290	AI846205	NM_146236
752	162460_f_at	0.006996	121.43	176.27	---	AV048486	NM_008784
753	116947_at	0.00701	532.37	782.3	2810430J06Rik	AW122218	NM_022424
754	114984_at	0.00708	2005.33	2436.1	---	AW121714	NM_028821
755	104258_at	0.00709	663.93	745.17	Acyp2	AA881576	NM_029344
756	164531_f_at	0.007102	768.1	1450.7	---	AV350397	NM_011106
757	107220_i_at	0.00711	204.5	278.47	---	AW259399	NM_133880
758	106935_at	0.007123	908.37	1301.9	1110001I14Rik	AI854179	NM_197985
759	107145_at	0.007147	1346.13	1574.73	Gga3	AI851469	NM_173048
760	116676_at	0.007159	3168.17	4726.17	Cdc42	AW125122	NM_009861
761	116414_at	0.007189	319.03	563.13	Rnf149	AI180528	NM_001033135
762	160477_at	0.007284	68.53	106.93	Ndufa4	AW046205	NM_010886
763	97925_at	0.007285	777.07	1042.13	Csnk1e	AB028241	NM_013767
764	164497_r_at	0.007286	4030.73	5066.57	---	AV281937	NM_012042
765	93874_s_at	0.007308	383.03	498.77	Il11ra2	U69491	NM_010549 /// NM_010550
766	161980_f_at	0.007311	23.97	54.6	---	AV373612	NM_013863
767	105497_at	0.007315	253.5	440.17	---	AA288034	---
768	104608_at	0.007326	140.93	238.3	---	AI854293	NM_053157
769	98563_f_at	0.007331	940.67	1092.37	Mcrs1	AF015309	NM_016766 /// XM_485475
770	94263_f_at	0.007358	2013.67	2417.77	---	D85570	NM_011187
771	92216_at	0.007361	277.43	574.33	Madh7	AF015260	NM_008543
772	114781_at	0.007362	344.63	525.13	Emilin3	AA823722	NM_153127
773	132131_at	0.007372	2588.73	3206.83	---	AI644408	---
774	106482_at	0.007377	719.7	1306.77	---	AI874856	NM_001004146
775	164195_at	0.007379	477.87	690.67	Smap1	AA103091	NM_028534
776	171391_at	0.007386	2282.87	3069.73		AV300858	NM_153580
777	161070_at	0.007419	644.37	870.8	Spred2	AI851250	NM_033523
778	99019_at	0.007428	562.7	753.13	Por	D17571	NM_008898
779	95120_at	0.007435	678.73	1132.2	Tm4sf13	AI837621	NM_025359
780	99442_at	0.007446	725.67	1035.83	Resp18	L34214	NM_009049
781	104428_s_at	0.007477	791.3	1357.13	Matk	D45243	NM_010768
782	164477_f_at	0.007536	1416.7	2191.83	---	AV245656	NM_001013256 /// NM_026889

Table 4

783	113580_at	0.007547	609.57	641.97	Cebpg	AI847655	NM_009884
784	96114_at	0.007573	309.7	410.87	Ppp1r1a	AW122076	NM_021391
785	96132_at	0.00758	503.2	829.9	AB023957	AB023957	XM_619546
786	103620_s_at	0.007605	435.3	737.9	Smn	U77714	NM_011420
787	108047_at	0.007646	446.8	546.7	2010003J03Rik	AI838379	NM_027236
788	96864_at	0.007661	358.8	494.9	AI648866	AI848770	NM_207207
789	109789_s_at	0.007674	663.83	858.13	---	AI550358	---
790	167666_r_at	0.007674	548.93	926.8	---	AV317380	NM_173867
791	93809_at	0.007683	1414.07	1660.8	Aup1	U41736	NM_001025446 /// NM_007517
792	106299_at	0.007685	315.43	415.77	2010103A03Rik	AI850527	NM_183316
793	134760_at	0.007691	675.47	996.13	1500010M24Rik	AI604782	XM_129661
794	113231_at	0.007702	184.97	265.13	1700123O20Rik	AI854099	NM_021437
795	103497_at	0.00772	70	124.63	BC025546	AA592351	NM_146215
796	109079_f_at	0.007722	2889.57	4017.63	5730446C15Rik	AI853578	NM_146096
797	169829_r_at	0.007732	537.03	936.47	---	AV151433	NM_013932
798	113606_at	0.007761	568.53	697.2	Syap1	AA691068	NM_025932
799	163171_at	0.007769	1229.8	1491.1	2610204M08Rik	AW125550	NM_198411
800	160894_at	0.007778	151.3	340.63	Cebpd	X61800	NM_007679
801	160963_at	0.0078	780.9	961.67	9630050M13Rik	AI551141	XM_194000
802	92610_at	0.007803	294.43	470.47	Rdbp	M21332	NM_138580
803	105512_at	0.007815	120.1	176.1	6330583I20Rik	AA190125	---
804	107364_at	0.007815	208.13	306.83	---	AW048457	---
805	164418_f_at	0.00783	529.07	730.33	---	AV062925	NM_147778
806	102786_at	0.007844	3839.5	4610.7	Clcn3	AI849432	NM_007711 /// NM_173876
807	168912_f_at	0.007844	13144.33	16194.93	---	AV013882	NM_010239
808	100438_at	0.007851	329.4	490.73	Gpr19	U46923	NM_008157
809	160572_at	0.007855	351.8	430.13	Dhx15	AF017153	NM_007839
810	113211_at	0.007872	350.93	706.47	BC023126	AW049974	NM_015807
811	93362_at	0.007888	8325.6	10665.77	Ap2m1	U27106	NM_009679
812	104534_at	0.007938	137.1	177.7	Pgm1	AA623874	NM_025700
813	97200_f_at	0.007984	899	1489.83	Snrpe	X65704	NM_009227
814	171010_at	0.007984	237.03	329.5	---	AV329897	---
815	160688_at	0.007986	748.67	1033.73	Golph3	AW060175	NM_025673
816	161184_f_at	0.007987	61.33	112.83	---	AV235418	NM_011587
817	102124_f_at	0.007996	312.27	529.93	---	AI836879	NM_009941
818	98492_at	0.007998	513.97	679.93	Cklfsf7	AA920419	NM_133978
819	93844_at	0.008001	5893.87	8172.17	1500040F11Rik	AW061302	NM_025352
820	163053_at	0.008004	1049.07	1526.43	Arhe	AA716925	NM_028810

Table 4

821	93190_at	0.008006	195.73	260.2	---	AW209179	XM_620267
822	166274_f_at	0.008032	2952.2	3558.3	1110061L23Rik	AV280207	NM_029406
823	98350_at	0.008045	327.07	449.6	Sstr2	AF008914	NM_009217
824	103467_g_at	0.008048	536.7	778.53	---	AA790056	NM_019396 /// NM_180962
825	94348_f_at	0.008055	1991.2	2457.5	Pcmt1	AW124044	NM_008786
826	94420_f_at	0.008055	467.1	600.87	Cry1	AB000777	NM_007771
827	99126_at	0.008066	155.43	504.5	---	L04961	NR_001463 /// NR_001570
828	109728_at	0.008078	1079.1	1483.8	Rtn3	AI848741	NM_175381
829	103960_at	0.008103	2047.27	2965.63	Rap2ip	U73941	NM_016759
830	165145_s_at	0.008103	1109.57	1577.57	---	AV358817	NM_007563
831	162549_at	0.008104	1146.93	1487.17	5031400M07Rik	AI464691	NM_020586
832	95123_at	0.008123	195.63	289.6	4930566A11Rik	AI844003	NM_029468
833	109016_at	0.008171	1068.33	1299.3	---	AI891634	XM_622387
834	170475_r_at	0.008181	511.23	837.6	---	AV211425	NM_008558
835	98975_at	0.008197	75.97	119.83	2410008G02Rik	AI019999	NM_172410
836	164045_at	0.008253	492.67	664.1	---	AV342167	NM_001013792
837	102807_at	0.008254	853	1059.87	9230112O05Rik	AW048054	NM_173347
838	104386_f_at	0.00827	3210.9	4422.4	Itgav	AI843901	NM_008402
839	111826_at	0.008272	2494.3	3225.7	Wasbp	AW047181	NM_030729
840	99444_at	0.008292	326.47	450.93	Ramp2	AJ250490	NM_019444
841	95963_at	0.008326	172.63	271.17	C77370	C77386	XM_205178
842	162938_at	0.008346	1029.97	1192.9	AI836810	AI836810	NM_172988
843	97277_at	0.008358	205.13	308.4	1810015M01Rik	AI844179	NM_026933
844	116642_f_at	0.008359	236.07	359.43	2310036D22Rik	AI852563	NM_027992
845	161243_f_at	0.00836	1456	1732.67	---	AV284333	NM_022419
846	129278_at	0.008361	414.2	1038.1	Pnkp	AI049061	NM_028398
847	116942_at	0.008416	1771.9	3087.77	Picalm	AI838939	NM_146194
848	97358_at	0.008422	5096.27	5992.47	Lphn1	AI851356	NM_181039
849	96322_at	0.008437	1120.57	1309.37	Edf1	AI836001	NM_021519
850	100042_at	0.008444	842.1	1056.7	Hagh	AI837921	NM_024284
851	113070_at	0.008457	830.7	1495.5	---	AA959975	NM_019775
852	163418_at	0.008473	378.2	511.47	---	AI121731	NM_011365
853	113451_at	0.00848	1197.43	1665.5	Dnmt3l	AA919800	NM_019448
854	95109_at	0.008519	552.03	703.33	Nol5a	AW121447	NM_024193
855	166210_i_at	0.008529	5310.4	5994	AI447711	AV256897	NM_207214
856	97296_at	0.008534	180.83	234.9	Mrpl44	AW124918	XM_357108
857	92291_f_at	0.008546	66.43	168.37	Cfhl1	M29008	NM_015780
858	104135_at	0.008562	720.73	839.43	Arl3	AW045474	NM_019718

Table 4

859	115883_g_at	0.008563	489.87	664.2	Mapk11	AW060873	NM_011161
860	167732_r_at	0.008574	862.8	1477.57	---	AV207429	---
861	164228_at	0.008584	1816.87	2403.97	Ces1	AI663823	NM_021456
862	163666_at	0.008594	410.53	748.33	6330404A12Rik	AW124064	NM_025696
863	92603_at	0.008621	4782.57	5469.87	Atp6v0d1	U13840	NM_013477
864	95412_at	0.008648	562.83	789.1	Pdcd6	U49112	NM_011051
865	106837_at	0.00865	269.03	435.6	---	AW048966	---
866	101542_f_at	0.008655	1074.8	1385.53	Ddx3x	L25126	NM_010028
867	105815_at	0.008655	344.8	804.5	---	AI851880	XM_137156
868	106255_at	0.008656	1443.77	1681.4	D10Ertd516e	AI840993	XM_125901
869	94907_f_at	0.008674	2361.97	3059.23	1110001J03Rik	AW045632	NM_025363
870	164797_f_at	0.008708	2473.3	2849.73	---	AV272434	NM_026203
871	167054_at	0.00872	547.73	819.43	---	AV027113	NM_026124
872	116009_at	0.008749	241.13	293.3	---	AA623188	---
873	112356_at	0.008774	363.1	644.63	---	AW061229	---
874	130799_at	0.008775	2158.87	2552.8	9130020K17Rik	AU023960	XM_619786
875	162125_f_at	0.008796	1052.97	1445.13	---	AV305832	NM_019639
876	94400_at	0.008826	1139.27	1353.2	1110051M20Rik	AI843094	NM_175123
877	116105_at	0.008874	1330.13	1917.47	A130092J06Rik	AA739339	NM_175511
878	101694_f_at	0.008877	144.13	222.03	Myst2	W91649	NM_177619
879	96113_at	0.008886	934.9	1327.3	D18Wsu98e	AI846519	NM_178604
880	113294_at	0.008917	849.47	1149.53	2810027J07	AW121913	NM_172617
881	164341_f_at	0.008918	121.67	219.2	---	AV245613	NM_181517
882	95721_at	0.008921	670.17	805.9	Mapkapk2	AW120722	NM_008551
883	112824_at	0.008924	953.2	1254.37	1110015K06Rik	AI847975	NM_026748
884	161396_f_at	0.008934	649.3	1046.87	---	AV271976	NM_173755
885	135744_at	0.008938	8318.3	14384.57	Jph3	AI849738	NM_020605
886	99925_f_at	0.008952	612.97	711.2	Tubg2	AI835567	NM_134028
887	94032_at	0.008976	1799.87	2360.63	Apoa1bp	AI845103	NM_144897
888	112313_at	0.008981	283.77	415.17	1110059G10Rik	AW123703	NM_025419
889	115844_at	0.008994	813.57	1038.47	1810008K03Rik	AI847028	NM_026929
890	164832_f_at	0.009059	1533.47	2047.67	---	AV337321	NM_172723
891	96899_at	0.009063	2941.93	3665.73	Ndufs3	AW123802	NM_026688
892	98936_at	0.009088	705.13	1003.93	Sars1	AI837395	NM_011319
893	164325_f_at	0.009116	488.1	772.53	BC006705	AV244930	NM_145404
894	103273_s_at	0.009181	207.83	362.13	Abcc8	AF037312	NM_011510
895	170984_at	0.009196	9192.43	11061.97	E330036L07Rik	AV139212	NM_144851
896	165009_f_at	0.00922	507.47	720.8	Cln2	AV000115	NM_009906

Table 4

897	94531_at	0.009239	669.77	960.67	2310005O14Rik	AW124582	NM_026452
898	101042_f_at	0.009278	184.17	296.67	Slc7a10	U51014	NM_008820
899	116303_at	0.00933	186.07	272.83	AI115454	AA592780	NM_032000
900	94043_at	0.009332	2996.47	3261.57	Atp6ap1	AB031290	NM_018794
901	115741_at	0.009363	472.03	580.27	Pik3cb	AW125843	NM_029094
902	96610_at	0.009392	1895.97	2472.33	Atp6v1h	AW046442	NM_133826
903	105402_at	0.009394	756.93	1083.57	---	AI390493	---
904	105802_at	0.009397	210.77	356.6	---	AI845876	---
905	113837_f_at	0.00941	689.43	896.97	Asb13	AA183628	NM_080857 /// NM_178283
906	163690_at	0.00943	307.87	447.27	Ednra	AI481591	NM_010332
907	98129_at	0.009437	4989.9	6702.63	---	AI852553	NM_025284
908	AFFX-PyruCarbMur/L09192_3_at	0.009446	1084.87	1452.6	Pcx	L09192	NM_008797
909	94367_at	0.009453	258.97	338.7	AA407809	AI850362	NM_030724
910	99101_at	0.009456	1165.97	1321.33	Eif3s7	AB012580	NM_018749
911	112445_at	0.009475	494.67	609.53	Slc39a14	AI156718	NM_144808
912	93581_at	0.009478	3145.37	4082.87	Ndufb8	AI845121	NM_026061
913	105276_f_at	0.009497	694.1	1444.9	---	AA414644	---
914	103964_at	0.009499	775.3	1002.7	Esrra	U85259	NM_007953
915	100225_f_at	0.009507	269.7	438.07	---	AA409481	NM_008948
916	171221_at	0.009507	870.27	1054.6	Gars	AV153208	NM_180678
917	100009_r_at	0.009511	1413.53	1823.27	Sox2	X94127	NM_011443
918	164990_f_at	0.009529	147.57	288.87	---	AV370077	NM_025556
919	103247_at	0.009533	480.9	632	Mpp3	AF079366	NM_007863
920	112703_at	0.009548	3194.8	4296.83	Eid2	AI846613	NM_198425
921	133820_at	0.009558	652.43	930.37	2810429C13Rik	AU044932	NM_176979
922	93008_at	0.009569	663.6	875.83	Lsm4	AW120557	NM_015816
923	94876_f_at	0.00958	1617.8	2019.8	Gorasp2	AI849207	NM_027352
924	92925_at	0.00958	292.43	410.87	Cebpb	M61007	NM_009883
925	109175_at	0.009654	1062.9	1433.13	2010311D03Rik	AI843827	NM_133839
926	113552_at	0.009656	1887.6	2215.97	2810405K02Rik	AI837737	NM_025582
927	111532_at	0.009657	1331.83	1813.67	2510002C16Rik	AW123028	NM_134134
928	164992_f_at	0.009671	1619.17	2185.23	---	AV228551	NM_025949
929	111491_at	0.009693	363.37	595.3	Klhl2	AI848030	NM_178633
930	109424_at	0.009697	750.67	1072	2410021P16Rik	AI196754	NM_028037
931	163512_at	0.009725	658.73	1689.77	Fosl2	AV371646	NM_008037
932	164012_at	0.009762	1174.93	1338.33	6330410P18Rik	AI156157	XM_203753
933	93975_at	0.009771	708.6	1007.9	1300002F13Rik	AI853531	NM_133753
934	116671_at	0.009771	899.87	1095.17	2700079M14Rik	AW123023	NM_145426

Table 4

935	101525_at	0.009777	2043.47	2642.67	Ndufb10	AI848871	NM_026684
936	161997_f_at	0.009783	81.37	137.07	---	AV329607	---
937	108908_at	0.009803	1631.87	1808.87	Arnt	AA222032	NM_009709
938	112850_at	0.009821	873.23	1278.03	2900002H16Rik	AW121352	NM_021430
939	168810_r_at	0.009829	562.83	744	---	AV269742	NM_138677
940	160690_at	0.009851	487.03	726.4	Csnk2a1	AW050240	NM_007788
941	167787_at	0.009858	809.13	1173.4	---	AV265048	---
942	134726_f_at	0.009859	479.03	773.57	Slc1a7	AA182154	NM_009201
943	135755_at	0.009871	524.9	832.77	2400009B08Rik	AI851656	XM_358687
944	167641_r_at	0.009908	540.07	915.6	0610012D17Rik	AV266358	NM_025329
945	161913_r_at	0.009927	7689.57	10294.83	---	AV378014	---
946	116400_at	0.009935	107.17	165.3	4632415D10Rik	AI842937	NM_030165
947	102364_at	0.009966	7584.37	11474.5	Jund1	J04509	NM_010592
948	109103_f_at	0.009981	324	466.2	1110038B12Rik	AI841088	XM_358504 /// XM_359415
949	169645_r_at	0.009984	244.33	449.73	---	AV305445	---
950	92790_at	0.01	149.83	229.73	Kpna2	D55720	NM_010655

Table 5

%Dark rearing versus control
%Upregulated in dark rearing
%Significance criterion = 0.01
%

%i	affyid	p	DR	control	gene		
1	109431_at	0.000001	1015.2	188.03	---	AW125135	---
2	130667_at	0.000001	1551.97	611.97	Epb4.1l3	AI848096	NM_013813
3	96496_g_at	0.000002	1804.17	787.3	Mytl1	U86338	NM_008666
4	104248_at	0.000003	1794.9	776.47	0610038P07Rik	AW227650	NM_026155
5	95978_at	0.000003	181.37	51.13	---	AA414964	XM_148700 /// XM_622655
6	112702_at	0.000003	690.83	172.67	Slc4a4	AI854341	NM_018760
7	115299_at	0.000004	1334.47	324.43	Bsn	AI426037	NM_007567
8	109408_at	0.000005	1019.33	758.7	---	AW046936	---
9	99076_at	0.000006	1259.67	572.5	Nr1d2	U09504	NM_011584
10	129294_at	0.000006	306.83	21.67	D130005A03	AI465241	NM_001009949
11	114445_at	0.000007	5457.13	2772.9	Atp8a1	AW125151	NM_009727
12	94740_g_at	0.000008	180.57	17.57	Trpc1	U73625	NM_011643
13	101362_at	0.000009	1765.1	372.17	Mapk9	AB005664	NM_016961 /// NM_207692
14	168095_at	0.00001	1387.73	292.33	Pafah1b2	AV116776	NM_008775
15	101837_g_at	0.000011	1714.7	519.13	Ppm1b	D45859	NM_011151
16	97760_at	0.000011	1063.17	219.17	Mtap2	M21041	---
17	107527_at	0.000011	3160.5	2187.3	---	AW121251	NM_054043
18	116912_at	0.000011	3500.63	1774.7	C530028O21Rik	AI843128	NM_175696
19	136256_at	0.000011	5537.2	3344.7	---	AI850930	---
20	131832_at	0.000014	5546.23	2060.23	0710001E19Rik	AW121426	NM_029716 /// NM_175752
21	93648_at	0.000015	4591.37	1818.67	Prkcc	L28035	NM_011102
22	106896_at	0.000016	1755	475.17	Zfp106	AW049892	NM_011743
23	136760_at	0.000017	3294.23	1716.03	Dtna	AI851910	---
24	95669_g_at	0.000019	5703.03	4154.53	Stmn2	AI840972	NM_025285
25	92910_at	0.000021	690.8	153.83	Arnt2	D63644	NM_007488
26	97104_g_at	0.000021	1019.27	537.9	0610038L10Rik	AF031380	NM_019437
27	139258_at	0.000021	13332.5	3207.7	Kif5a	AW050241	NM_008447
28	103275_at	0.000023	3618.8	1179.97	Atp6v0a1	U13836	NM_016920
29	138070_at	0.000023	26107.07	16220.37	Sv2b	AW045524	NM_153579
30	104269_at	0.000024	2566.5	2013.4	Tnnt1	AB026806	NM_016908
31	163382_at	0.000024	1851.57	281.2	4121402D02Rik	AA791958	NM_028722
32	93496_at	0.000025	2412.97	1456.13	Elovl5	AI852098	NM_134255

Table 5

33	114611_at	0.000026	1774.7	416.93	Ids	AA637320	NM_010498
34	105790_at	0.000026	3650.63	1611.77	Pcdh10	AI842344	NM_011043
35	139157_at	0.000027	1937.63	1151.07	---	AW123263	---
36	106938_at	0.000028	585.6	203.1	4930469P12Rik	AW227323	NM_021284
37	167002_at	0.000029	1796.07	719.93	9630038C02Rik	AI853123	NM_172961
38	104244_at	0.00003	930.37	442.7	Mark2	AI606891	NM_007928
39	107293_at	0.000034	2733.4	1102.6	Hspa12a	AW048913	NM_175199
40	140695_f_at	0.000034	3002.8	958.2	---	AW122309	---
41	140638_at	0.000036	1297.23	747.93	---	AW125813	NM_010926
42	135796_at	0.000037	990.17	661.2	---	AI842144	NM_018797
43	93339_at	0.000038	571.1	370.97	---	AI846243	NM_008575
44	105307_at	0.000038	2419.5	829.17	Cpeb4	AI585962	NM_026252
45	99163_at	0.000039	2823.07	332.03	---	AI844232	XM_356498
46	104330_g_at	0.000039	542.53	229.3	Smarcf1	AI842326	NM_033566
47	96587_at	0.000039	1867.43	349.27	Arf3	D87900	NM_007478
48	160772_i_at	0.000039	771.23	340.97	D11Ertd730e	AW214428	NM_148673 /// NM_198936
49	109123_at	0.000039	3832.97	2492.47	2900029G13Rik	AI839366	NM_175274
50	129184_at	0.000039	4436.63	1605	F830029L24Rik	AI414773	NM_172606
51	108576_at	0.00004	463.43	181.17	Lsm6	AI836373	XM_134104
52	133116_at	0.00004	1980.83	351.43	Edil3	AA754682	NM_010103
53	100418_at	0.000041	294	197.17	Gng2	AW123750	NM_010315
54	99645_at	0.000042	3553.47	1910.33	4921506J03Rik	AW048484	XM_356498
55	163579_at	0.000043	3509.03	1610.27	Gpr88	AI852526	NM_022427
56	134082_at	0.000047	4277.67	1006.9	Ube2n	AA866989	NM_080560
57	167905_f_at	0.000047	5701.43	1728.97	Flrt3	AV240055	NM_178382
58	166599_at	0.000048	379.97	253.57	Nr2e1	AU046154	NM_152229
59	95804_g_at	0.000049	2510.8	765.83	Ptpns1	D85785	NM_007547
60	93604_f_at	0.00005	6504.03	1017.73	Igsf4	AF061260	NM_001025600 /// NM_018770 /// NM_207675 /// NM_207676
61	171190_f_at	0.00005	1401.53	467.33	---	AV118515	NM_011857
62	130413_at	0.000051	1348.57	285.7	2310047C04Rik	AU014930	XM_148605 /// XM_358866
63	112453_at	0.000052	609.2	367.47	Edem1	AW048464	NM_138677
64	117173_s_at	0.000053	499.53	182.03	1500004A08Rik	AI550395	NM_178149
65	105787_at	0.000054	619.1	300.07	Fgd4	AI837350	---
66	135258_at	0.000054	5078.57	1045.47	---	AI848604	---
67	96606_at	0.000055	1166.7	428.73	1500003O03Rik	AB025217	NM_019769
68	103745_at	0.000056	553.77	200.87	Snx13	AW227027	NM_001014973
69	93895_s_at	0.000056	1509.67	718.1	Itpr1	M21530	NM_010585
70	132102_at	0.000056	2164.1	1057.23	MGC79213	AI593250	NM_198625

Table 5

71	92659_at	0.000057	847.03	278.5	5730402K07Rik	AF115480	NM_019688	
72	163972_at	0.000058	1187.83	894.93	Pxmp4	AI648762	NM_021534	
73	129436_at	0.000059	668.17	152	2900057D21Rik	C88264	NM_145221	
74	92508_s_at	0.000063	400.97	115.73	Utrn	X83506	NM_011682	
75	115455_at	0.000063	1287.07	372.73	---	AI875522	NM_010243	
76	112680_at	0.000063	2211.8	492.23	Ssbp3	AI835469	NM_023672 /// NM_198438	
77	114065_at	0.000064	8150.07	3030.8	Scrg3	AW046758	XM_193795	
78	93188_at	0.000065	2628.27	1197.6	Dkk3	AJ243964	NM_015814	
79	97184_at	0.000065	367.07	268.5	BC023106	AI528219	NM_145476	
80	163408_at	0.000065	839.8	263.27	Apc	AW121617	NM_007462	
81	164243_at	0.000065	820.93	290.43	4930515K21Rik	AI597519	NM_133817	
82	103434_at	0.000066	269.07	30.73	Pscd3	AF001871	NM_011182	
83	160098_s_at	0.000068	515.23	298.6	Cryab	AI842724	NM_007983	
84	108893_at	0.000069	1749.83	419.23	Mef2a	AI060854	NM_001033713	
85	164225_at	0.000069	805.9	201.03	Clasp1	AI616095	---	
86	98890_at	0.000073	600.33	306.87	1700012G19Rik	AI848173	NM_025954	
87	107928_at	0.000073	588.77	277.33	Stk2	AI874509	NM_009289	
88	AFFX-TransRecMur/X57349_3_at	0.000074	1374.33	399.7	Trfr	X57349	NM_011638	
89	99511_at	0.000075	1485.03	896.9	Prkcb	X53532	NM_008855	
90	116697_at	0.000075	2504.77	813.07	4930415J21Rik	AA427047	NM_177767	
91	100320_at	0.000076	186.93	33.4	Kpna4	AF020771	NM_008467	
92	114801_at	0.000077	1230.87	610.93	---	AI846867	---	
93	105584_at	0.000083	827.97	383.83	2410014A08Rik	AI604793	NM_175403	
94	140851_at	0.000084	1372.9	897.97	---	AW213569	---	
95	114569_at	0.000085	280.37	80.3	C630029K18Rik	AW123047	NM_144871	
96	97017_f_at	0.000086	503.73	437.13	---	AW214439	---	
97	166833_at	0.000088	97625.93	43465.37	Nrgn	AI837453	NM_022029	
98	168346_r_at	0.000088	10192.43	3403.9	Syt11	AV283445	NM_018804	
99	105742_at	0.00009	2116.5	1097.83	Sdccag8	AI835291	NM_011785	
100	103092_at	0.000091	3206.5	1120.93	Trim37	AW124316	NM_197987	
101	166658_at	0.000091	2373.83	1415.47	---	AI047433	NM_010636	
102	134288_at	0.000093	439.2	22.83	Macf1	AI551319	XM_110503	
103	109781_at	0.000094	2038.87	951.67	D030063F01Rik	AW121178	NM_133766	
104	114683_at	0.000094	2627.37	2266.83	C330002I19Rik	AW125126	XM_126866	
105	107453_at	0.000094	2768.77	1875	Ube2n	AW122034	NM_080560	
106	139227_at	0.000095	1845.73	852.03	1810055P05Rik	AW048554	NM_011560 /// NM_198104	
107	114139_at	0.000096	586.97	157.87	---	AI843123	NM_010274	
108	113045_at	0.000096	653.37	115.17	Wasl	AW210253	NM_028459	

Table 5

109	130757_at	0.000096	3253.77	1020.97	1110035G07Rik	AW122018	NM_001008791 /// NM_001008792 /// NM_001008793 /// NM_001008794 /// NM_001008795 /// NM_001008796 /// NM_001008797 /// NM_001008798 /// NM_028640
110	137158_i_at	0.000097	913.9	50.47	9630005B12Rik	AI042790	NM_013862
111	106101_at	0.000098	1918.33	1033.1	9030406N13Rik	AI853221	NM_172495
112	138205_at	0.000098	4475.37	1875.8	---	AW050055	---
113	104504_at	0.0001	1072.1	371.53	Scn8a	U26707	NM_011323
114	112820_at	0.0001	2045.23	1714.63	Rnf123	AW045244	NM_032543
115	117054_at	0.0001	2262.6	543.87	Tpm1	AI854628	NM_024427
116	117280_at	0.0001	1822.47	1084.37	Pknox2	AI835075	NM_001029838 /// NM_148950
117	166635_i_at	0.000101	810.83	80.33	Hrasls	AI427922	NM_013751
118	99423_at	0.000102	486.77	77.8	---	L39373	NM_010795
119	138539_at	0.000103	25290.87	18800.27	Atp2b2	AI846952	NM_009723
120	141042_at	0.000103	1126.43	128.13	2810468K05Rik	AA794456	XM_484053
121	93784_at	0.000104	953.57	659.9	Cfdp	AB010828	NM_011801
122	111518_at	0.000104	7320.6	5145.43	D12Ertd553e	AA170647	NM_029758
123	166393_at	0.000105	369.83	143	AI836376	AV261405	NM_178896
124	113546_at	0.000106	2576.27	1957.3	---	AI853303	NM_023625
125	165460_at	0.000106	17678.13	8293.6	Syt11	AI853126	---
126	AFFX-TransRecMur/X57349_3_at	0.000108	631.47	248.57	Trfr	X57349	NM_011638
127	113933_at	0.000109	2996.6	1285.63	AA959742	AI789270	NM_133807
128	168252_f_at	0.000109	1819.6	435.03	4933409K03Rik	AV267393	XM_355251
129	110301_at	0.00011	1656.13	463.5	Tes3	AI854850	NM_033623
130	94739_at	0.000111	620.43	246.67	Trpc1	U73625	NM_011643
131	101757_at	0.000112	1224.2	640.7	---	AF015881	NM_008686
132	110240_g_at	0.000112	1321.67	500.9	2210402G22Rik	AW124610	NM_144516
133	129225_at	0.000112	7652.8	3319.6	---	AI427087	NM_010014 /// NM_177259
134	109326_at	0.000113	5621.23	2932.8	Epb4.1l1	AI837923	NM_001003815 /// NM_001006664 /// NM_013510
135	106815_at	0.000115	417.23	134.17	Ppm1l	AW047326	NM_178726
136	104499_at	0.000116	355.53	101.77	Homer1	AB019479	NM_011982 /// NM_147176 /// NM_152134
137	116873_at	0.000116	3264.07	1389.63	D9Bwg0185e	AI844641	NM_173781
138	106910_at	0.000117	1026	672.33	Add2	AW048717	NM_013458
139	108305_at	0.000118	2642.13	1546.23	C130068N17	AA123481	NM_177784
140	116833_at	0.000119	1524.57	462.13	2210409H23Rik	AW125281	---
141	138127_at	0.000121	1515.57	672.73	Trim2	AW048197	NM_030706
142	167881_at	0.000122	2753.23	445.93	4930415J21Rik	AW124395	NM_177767
143	166137_at	0.000123	1884.83	495.03	Ap1gbp1	AA672253	NM_194341
144	105739_at	0.000124	1697.5	465.47	Hspa12a	AI853180	NM_175199
145	111178_at	0.000124	1419.83	332.67	Dcamkl1	AI854218	NM_019978

Table 5

146	93498_s_at	0.000125	6078.27	2278.2	Aplp2	M97216	NM_009691
147	99883_g_at	0.000125	979.83	287.63	Ids	L07921	NM_010498
148	169000_at	0.000126	571	106.77	Pik4ca	AV119893	NM_001001983
149	163739_at	0.000128	2869.6	588.6	Mef2c	AW124472	NM_025282
150	163387_at	0.000129	1927.5	741.5	Dpp8	AA982295	NM_028906
151	106295_at	0.00013	3232.33	2261.97	5430432P15Rik	AI843462	XM_129246
152	113431_at	0.000134	1815.47	733.17	Rnf14	AI121269	NM_020012
153	102277_at	0.000135	431.67	119.03	Zfp26	M36514	XM_134736
154	104249_g_at	0.000135	1160.4	193.4	0610038P07Rik	AW227650	NM_026155
155	92209_at	0.000135	815.63	386.17	Ulk1	AF053756	NM_009469
156	99893_at	0.000136	808.9	139.93	Fgf13	AF020737	NM_010200
157	95512_at	0.000137	1904.8	1419.87	Pcmt1	M60320	NM_008786
158	165696_at	0.000138	5862.3	2054.07	Dnm1l	AI450666	NM_001025947 /// NM_152816
159	163214_at	0.000139	1179.33	723.17	---	AA960020	---
160	137492_at	0.000141	1732.2	624.87	Birc4	AI606147	NM_009688
161	165556_at	0.000141	951.27	665.6	4930444A02Rik	AI854270	NM_029037
162	112732_g_at	0.000142	1824.27	937.27	Pkp4	AI315672	NM_026361
163	98864_s_at	0.000146	383.4	115	Grik2	D10054	NM_010349
164	114363_at	0.000146	6505.5	5513.23	Acvr1b	AI851648	NM_007395
165	116853_at	0.000146	3334.43	1721.87	---	AA672555	NM_183028
166	167286_at	0.000149	2842.6	698.8	Rab11a	AV009116	NM_017382
167	140247_at	0.00015	911.63	210.3	D130060C09Rik	AI848011	NM_177054 /// NM_199038
168	94854_g_at	0.000151	7032.97	3553.6	Gnb1	U29055	NM_008142
169	110390_g_at	0.000151	564.83	210.97	Gspt1	AI785722	NM_146066
170	163558_at	0.000151	8112.3	4596.47	Faim2	AI842701	NM_028224
171	115180_at	0.000153	1026.8	185.2	0610013E23Rik	AA727727	NM_028259
172	93527_at	0.000154	1448.53	520.03	Bteb1	Y14296	NM_010638
173	105869_at	0.000156	1170.3	571.43	---	AI849944	NM_020253
174	109986_at	0.000157	768.1	403.83	Epm2aip1	AI648034	NM_175266
175	110641_at	0.000159	2077.33	770.37	4930438M06Rik	AI597241	NM_145564
176	111420_at	0.000161	8350.4	6084.4	Atp6v0a1	AI848960	NM_016920
177	128645_at	0.000161	1747.2	468.8	---	AW125499	XM_488300
178	112431_at	0.000162	493.47	207.43	A230103N10Rik	AI853946	NM_212484
179	102259_at	0.000164	2194.8	329.13	Ywhag	AF058799	NM_018871
180	115077_f_at	0.000166	607.7	362.7	Dbt	AA896722	---
181	116155_at	0.000166	1827.93	969.8	9530003A05	AW121754	XM_129375
182	93908_f_at	0.000167	876.33	392.37	---	X16670	XM_620701
183	106590_at	0.000168	5820.93	3218.17	5930405J04Rik	AW120782	NM_198160

Table 5

184	164139_at	0.000168	2143.8	699.3	Sv2b	AV266519	NM_153579
185	110642_at	0.00017	427.23	226.17	Hp1bp3	AA656401	NM_010470
186	105349_at	0.00017	685.23	263.6	---	AI850082	NM_007561
187	92642_at	0.000171	3194.73	2320.5	Car2	M25944	NM_009801
188	101933_at	0.000172	576.77	316.67	Rab10	AF035646	NM_016676
189	139156_at	0.000172	511.97	299.3	4931417E21Rik	AW123123	XM_132812
190	105480_at	0.000174	566.47	273.93	D6Bwg1452e	AW108322	XM_143984
191	93882_f_at	0.000175	571.9	152.2	Tgoln1	D50032	NM_009443 /// NM_009444
192	140488_i_at	0.000176	994.67	212.63	1500012D09Rik	AW060560	NM_172601
193	106895_at	0.000177	949.6	585.7	Adcyap1r1	AW049850	NM_001025372 /// NM_007407
194	136692_at	0.000178	2878.47	1420.67	---	AI854543	---
195	114748_at	0.000179	1084.37	572.97	Dapk1	AI853387	NM_029653
196	138922_g_at	0.00018	20952.8	5218.8	Atp6v0a1	AI481492	NM_016920
197	106015_at	0.000182	746.5	392.6	---	AI854204	NM_145553
198	111170_at	0.000182	306.37	102.63	---	AI877190	NM_019663
199	AFFX-GapdhMur/M32599_M_at	0.000182	108549.97	70272.6	Gapd	M32599	NM_001001303 /// NM_001001978 /// NM_008084 /// NM_199472 /// XM_139510 /// XM_195823 /// XM_204942 /// XM_354601 /// XM_356092 /// XM_356116 /// XM_357991 /// XM_359225 /// XM_483878 /// XM_483891 /// XM_483995 /// XM_484256 /// XM_484307 /// XM_484345 /// XM_484436 /// XM_484654 /// XM_484732 /// XM_484834 /// XM_485043 /// XM_485318 /// XM_485562 /// XM_485937 /// XM_486133 /// XM_486264 /// XM_486386 /// XM_486623 /// XM_486720 /// XM_486749 /// XM_486779 /// XM_487067 /// XM_618752 /// XM_618821 /// XM_618960 /// XM_619006 /// XM_619136 /// XM_619142 /// XM_619144 /// XM_619236 /// XM_619350 /// XM_619822 /// XM_619956 /// XM_619966 /// XM_620176 /// XM_620348 /// XM_620482 /// XM_620523 /// XM_620532 /// XM_620646 /// XM_621075 /// XM_621114 /// XM_622431 /// XR_000341
200	128839_at	0.000184	622.3	391.83	---	AA863520	NM_178708
201	113250_at	0.000187	7646.9	4749.77	5830461H18Rik	AI847212	NM_029519
202	168099_at	0.000187	5165.6	1887.53	Prickle1	AV247559	XM_128308
203	110586_at	0.00019	522.37	186.97	3110035P10Rik	AA231297	NM_172445
204	105228_at	0.000194	1116.2	457.47	Man1b	AI528764	NM_010763
205	111540_at	0.000195	1027.5	627.57	1700021K19Rik	AA672508	NM_172615
206	101961_at	0.000197	1595.17	1273.87	Bub3	U67327	NM_009774
207	96747_at	0.000197	647.27	515.5	Arhu	AW121294	NM_133955
208	111741_at	0.000202	933.43	451.77	Gprc5b	AW123268	NM_022420
209	108381_at	0.000203	771.57	384.87	2410004N11Rik	AA981618	XM_622095
210	92944_at	0.000204	1260.7	351.7	Gria1	AW048549	NM_008165
211	114881_at	0.000204	1597.07	454.13	1110007A06Rik	AI841970	NM_024288
212	140418_at	0.000204	922.7	562.03	9130023F12Rik	AW124495	NM_001025106 /// NM_177672
213	94273_at	0.000205	1039.67	496.87	2610311I19Rik	AI849067	NM_023311
214	112781_at	0.000207	16343.83	7562.8	Syt11	AI841363	NM_018804
215	167869_f_at	0.000208	13496.93	6051.37	---	AV354082	NM_001007596 /// NM_153457

Table 5

216	132127_at	0.000209	1310.97	773.43	---	AI430959	---
217	111916_at	0.00021	1653.2	1165.33	Hmg20a	AI841396	NM_025812
218	107489_at	0.00021	3153.67	1138.2	Sort1	AW047183	NM_019972
219	138965_at	0.00021	1697.23	699.6	Dgkg	AI854428	NM_138650
220	98339_at	0.000213	2622.2	986.3	Syt11	AB026808	NM_018804
221	99023_at	0.000214	827.93	465.07	Pafah1b2	U57747	NM_008775
222	96679_at	0.000215	769.03	145.27	Dnajb9	AW120711	NM_013760
223	101447_at	0.000215	839.8	282.83	Apc	M88127	NM_007462
224	132578_at	0.000215	730.57	273.1	AK129128	AU024457	XM_127430
225	96583_s_at	0.000217	3475.17	534.3	Kif5a	AF053473	NM_008447 /// NM_008449
226	115191_at	0.000218	504.63	177.23	3732409C05Rik	AA693285	NM_026143 /// NM_027379
227	112331_at	0.000219	6646.47	4733.83	Fbxw7	AI847315	NM_080428
228	117166_at	0.000219	1980.9	869.4	Cpd	AI844013	NM_007754
229	100923_at	0.00022	395.4	192.37	Myo10	AJ249706	NM_019472
230	160934_s_at	0.00022	493.6	82.83	---	X05546	---
231	96007_at	0.000222	2100.73	1435.87	0610038P07Rik	AI835359	NM_026155
232	95530_at	0.000222	1086	569.27	Gtf2a1	AW060250	---
233	94388_at	0.000228	314.3	195.57	Ap3s2	U91933	NM_009682
234	110760_at	0.000229	1121.23	535.23	Zfp198	AI047555	NM_029498
235	117093_at	0.00023	672.7	339.33	C630028C02Rik	AW121637	NM_010014 /// NM_177259
236	139979_at	0.00023	2652.43	1420.37	Ndufs1	AI450646	NM_145518
237	108867_at	0.000233	2481.37	1459.6	Hnt	AW120667	NM_172290
238	132798_at	0.000234	1492.5	493.6	3526402J09Rik	AW060344	---
239	97369_g_at	0.000235	629.27	227.9	Akap1	U95145	NM_009648
240	111805_at	0.000237	1919	820.3	3930401K13Rik	AA939532	NM_028720
241	99492_at	0.000238	826.87	705.33	Catnbip1	AI851990	NM_023465
242	99528_at	0.000238	477.8	160.83	Spin	AW122015	NM_011462 /// NM_146043
243	107922_at	0.000238	474.63	113.33	Rnf141	AI226152	NM_025999
244	99981_at	0.000239	293.6	132.73	Gnaq	M55412	NM_008139
245	114302_at	0.00024	3346.67	1963.67	Csnk1e	AI049103	NM_013767
246	165560_at	0.000245	8329.87	4944.5	BC006583	AI850946	XM_485735
247	108353_at	0.000246	1709.37	780.37	Ppp2r5a	AA764532	NM_144880
248	105547_at	0.000247	654.3	451.23	---	AA797756	---
249	160111_at	0.000248	1308.93	586.1	1500010B24Rik	AI849718	NM_025437
250	167483_at	0.000248	4322.8	2511.5	Ndfip1	AV205835	XM_128893
251	98535_at	0.000251	1105.1	671.1	Comt	AF076156	NM_007744
252	104652_at	0.000252	1645.5	1027.7	Kcnk2	AI849601	NM_010607
253	135511_at	0.000252	2091.9	1054.73	1700020O03Rik	AA472944	NM_027405

Table 5

254	163845_i_at	0.000255	906.73	378.67	9130403P13Rik	AA387607	NM_026345
255	104449_at	0.00026	5166.73	2857.3	Glrb	X81202	NM_010298
256	107277_at	0.00026	1198.83	430.93	Hdh	AW045728	NM_010414
257	108306_at	0.00026	365.57	187.93	---	AI616225	XM_145254
258	131850_at	0.000266	1030.9	288.37	---	AW123206	---
259	92947_s_at	0.000267	12583.77	8200.83	Gria2	X57498	NM_013540
260	102927_s_at	0.000268	821.67	530.3	Hdh	L23312	NM_010414
261	163922_at	0.000269	321.57	127.1	Lats2	AI427338	NM_015771
262	104609_at	0.000271	931.63	499.67	Bscl2	AA644817	XM_355145
263	116515_at	0.000271	309.7	146.43	D330025I23Rik	AI509331	NM_173413
264	137692_at	0.000275	776.43	84	Akap6	AW049286	XM_484140
265	115477_at	0.000276	723.37	228.67	F830020C16Rik	AI006067	NM_177338
266	134102_at	0.000277	1741.43	634.07	Mdm2	AU023747	NM_010786
267	94913_at	0.000279	1356.83	613.9	AA409541	U65313	NM_011816
268	114896_at	0.000279	525.67	409	Glcci1	AU021420	NM_133236 /// NM_178072
269	162765_at	0.000279	916.63	361.23	Add3	AI852237	NM_013758
270	95664_at	0.000281	568.13	220.03	Sec14l1	AW048159	NM_028777
271	96539_at	0.000281	479.8	301.53	1200009K13Rik	AW212071	NM_025814
272	93700_at	0.000285	6573.47	2945.9	Arf3	AI838022	NM_007478
273	112345_at	0.000285	8199.5	5485.7	Ppp1r9b	AI841610	NM_172261
274	166510_r_at	0.000285	2102.27	421.07	D130060C09Rik	AV276560	NM_177054 /// NM_199038
275	131873_at	0.000294	2415.17	726.8	Gabra2	AW124947	NM_008066
276	111232_at	0.000297	770.07	80.57	2410018I08Rik	AW123718	NM_177561
277	97793_at	0.000298	640.63	168.9	Gria3	AB022342	NM_016886
278	100365_at	0.000298	250.7	31.07	Syt7	AB026804	NM_018801 /// NM_173067 /// NM_173068
279	138199_i_at	0.000298	2361.97	1067.47	D130029J02	AW048648	XM_150103
280	131405_at	0.000299	5714.6	3097.17	4930526B11Rik	AI851634	XM_204287
281	105423_at	0.000306	415.03	116.77	Rcbtb1	AI662508	NM_027764
282	160344_at	0.000307	1042.07	723.17	Npc2	AB021289	NM_023409
283	137987_at	0.000308	822.1	347.6	Rasgrf1	AI844718	NM_011245
284	137611_at	0.00031	4783.93	1667.27	4931406N15Rik	AI837243	NM_027629
285	112432_at	0.000312	2816.87	2191.1	Satb1	AW045567	NM_009122
286	136221_at	0.000312	2838.4	479.43	Slc4a10	AI835684	NM_033552
287	138565_at	0.000313	2856.07	2220.77	---	C85956	NM_019445
288	98004_at	0.000319	1061.37	290.6	Pkia	M63554	NM_008862
289	167218_at	0.000321	4804.4	2210.83	A130073L17Rik	AI837419	XM_126776
290	112817_at	0.000322	845.57	520.93	1810031K17Rik	AI854054	NM_026977
291	106181_at	0.000324	14637.77	4997.03	Ndr4	AI853311	NM_145602

Table 5

292	132021_at	0.000325	2622.4	570.1	C630030B20	AI429239	XM_357332
293	113595_at	0.000329	859.3	341.27	5330414D10Rik	AI852519	NM_153594
294	162991_at	0.000329	2713.83	1723.3	9130213B05Rik	AW108293	NM_145562
295	136105_at	0.000334	1686.23	853.83	Prdx1	AI845509	NM_011034
296	164005_at	0.000336	4891.2	2070.17	Spg3a	AV326112	NM_178628
297	106462_g_at	0.000338	837.87	352.67	5730402K07Rik	AI842094	NM_019688
298	136664_at	0.000339	552.63	182.83	Slc17a6	AI847452	NM_080853
299	138547_at	0.00034	6422.33	1552.33	Adcy1	AI849749	NM_009622
300	111427_at	0.000341	2260.03	852.1	D030028O16Rik	AI852560	NM_145984
301	117224_g_at	0.000342	2888.67	885	---	AI843176	---
302	108995_at	0.000342	966.67	444.77	BC030477	AA763904	NM_177618
303	97908_at	0.000349	2402.13	1944.87	1110007A06Rik	AW120676	NM_024288
304	99897_at	0.00035	891.73	306.9	Gabrb3	U14420	NM_008071
305	115117_at	0.00035	648.8	181.2	Ubqln2	AW047574	NM_018798
306	106455_at	0.00035	16418.9	7427.33	2900052E22Rik	AI846460	NM_182993
307	138421_at	0.00035	1631.87	857.23	Luzp1	AW125183	NM_024452
308	111414_at	0.000356	2090.5	1031.07	AI663987	AI840109	NM_033526
309	114061_at	0.000357	1115.87	518.67	Ppp2r5e	AI851550	NM_012024
310	130540_at	0.000359	7102.3	1331.17	D9Bwg0185e	AI845726	NM_173781
311	101140_at	0.00036	221.63	144.87	Htr1a	U39391	NM_008308
312	95614_at	0.000361	955.6	318.83	Cbx5	AI852086	NM_007626
313	163304_at	0.000361	471.5	320.1	Jmj	AW124791	NM_021878
314	99160_s_at	0.000363	7377.87	4792	1110025J15Rik	AW227647	NM_023168
315	107056_at	0.000363	1332.17	373.1	4931406N15Rik	AI837680	NM_027629
316	140696_f_at	0.000363	2946.9	443.67	---	AI837604	---
317	AFFX-PyruCarbMur/L09192_5_at	0.000367	1047.43	606.07	Pcx	L09192	NM_008797
318	93711_at	0.000368	1170.37	304.93	Sec23a	D12713	NM_009147
319	92294_at	0.00037	591.5	190.37	2810410P22Rik	AW060793	NM_182994
320	169258_i_at	0.000372	3470.2	1262.87	4631427C17Rik	AV296904	NM_021414
321	95393_at	0.000373	1252.97	358.3	Btbd3	AI503362	NM_001025431 /// NM_145534
322	116857_at	0.000377	12925.97	5727.4	Mtap1a	AI854162	XM_619804
323	94341_at	0.000378	1046.13	769.63	Jmj	D31967	NM_021878
324	163828_at	0.000378	689.77	369.27	AW556347	AW123626	NM_183186
325	135199_at	0.000378	883.63	212.4	Tnfrsf19	AI551729	NM_013869
326	138046_at	0.000381	1537.77	1178.07	---	AI843878	NM_133934
327	164000_at	0.000384	1426.23	751.57	1110018G07Rik	AI596405	NM_178065
328	138987_g_at	0.000384	2107.8	937.2	Centg3	AI847278	NM_139153
329	100398_at	0.000385	257.63	124.9	Kif3a	D12645	NM_008443

Table 5

330	111112_at	0.000385	1354.93	285.83	Hspa12a	AW124720	NM_175199
331	108865_at	0.000388	498.9	285.03	---	AW146426	---
332	93163_at	0.000392	5100.8	3202	Gabrg2	M62374	NM_008073 /// NM_177408
333	113696_at	0.000393	237.53	70.5	Ireb2	AA793873	NM_022655
334	112707_at	0.000393	614.47	347.97	Tnrc15	AW261668	NM_146112
335	113031_at	0.000394	1200.57	300.43	---	AI132545	NM_172522
336	163838_at	0.000396	1869.77	1088.4	Mtmr4	AA543943	NM_133215
337	115153_at	0.000398	1430	782.27	Zfp148	AI789647	NM_011749
338	135743_at	0.000398	2344.53	650.23	---	AI849654	NM_010103
339	104052_at	0.000402	1711.63	1208.43	1810011K17Rik	AI840921	NM_145513
340	95601_at	0.000403	1261.93	606	Ubqln1	AW125420	NM_026842 /// NM_152234
341	163538_at	0.000403	124.8	57.53	Fem1c	AI593805	NM_173423
342	166551_at	0.000405	7197.1	3511.53	Mtap1a	AI413403	XM_194040
343	138451_at	0.000407	7605	3063.07	4831417L10	AI852890	---
344	100510_at	0.000408	13068.83	4146.97	Sncb	AI839708	NM_033610
345	110267_g_at	0.000409	3009.73	2269.53	2900010D03Rik	AI153089	NM_201226
346	114322_at	0.00041	5420.6	3840.87	C330021A05Rik	AI843036	NM_153082
347	113684_at	0.000413	1617.2	1335.63	Ncbp2	AI847503	---
348	117111_at	0.000416	303.97	136.33	AI605202	AI837669	NM_207209
349	100323_at	0.000418	3460.33	1382.7	---	Z23077	NM_007444 /// NM_009665 /// XM_483892 /// XM_619503
350	98439_at	0.00042	547.63	207.43	2610318I15Rik	AW049356	NM_028259
351	96563_at	0.00042	439.67	170.57	2810030C21Rik	AI414051	XM_131566
352	106920_at	0.00042	2360.43	1587.3	Ncoa1	AI841750	NM_010881
353	165743_at	0.000421	14084.1	8165.3	Syn2	AI836018	NM_013681
354	115347_at	0.000422	694.23	408.7	2700078E11Rik	AI639571	NM_030197
355	138057_at	0.000424	1697.1	476.53	1500003N10Rik	AI837225	NM_001007154 /// NM_028806
356	132374_at	0.000425	7160.73	1927.8	2900042E17Rik	AI467276	NM_172653
357	106080_at	0.000426	6044.47	3825.43	Trim37	AW125666	NM_197987
358	92890_at	0.000429	1440.27	412.67	Kif1a	D29951	NM_008440
359	162689_at	0.000431	2918.67	1041.63	Rbm9	AI840070	NM_053104 /// NM_175387
360	166598_r_at	0.000432	1089.83	681	Pip5k3	AV290541	NM_011086
361	166370_at	0.000433	1836.97	394.1	Scamp1	AW120713	NM_029153
362	101198_at	0.000439	6689.77	3970.63	Cplx1	D38614	NM_007756
363	109143_at	0.000441	2910.9	1233.03	2410127E18Rik	AI848362	NM_029742
364	107914_at	0.000441	1446.3	671.27	9130213B05Rik	AW120948	NM_145562
365	111200_at	0.000442	170.4	109.5	Parva	AA726446	NM_020606
366	111293_at	0.000445	160.93	22.43	5832424M12	AI037539	NM_172591
367	160871_at	0.000447	629.57	170.37	Kif1b	AB023656	NM_008441 /// NM_207682

Table 5

368	94645_at	0.000448	281.6	52.8	Gabra3	M86568	NM_008067
369	105841_at	0.000448	618.57	135.77	9030612M13Rik	AI839453	NM_172458
370	112695_at	0.00045	1011.3	594.27	---	AW259285	---
371	98915_at	0.000452	715.9	198.77	Rnf149	AI849082	---
372	136679_at	0.000456	1136.63	280.77	Bicd1	AI852443	NM_009753
373	104031_at	0.000458	398.53	288.87	Ptch	U46155	NM_008957
374	116868_at	0.000459	3944.53	2004.33	Pja2	AI849505	NM_001025309 /// NM_144859
375	105223_at	0.000459	433.43	147.93	9530003A05	AI849923	XM_129375
376	111103_at	0.000459	1173.03	619.57	A030003E17Rik	AI021244	---
377	98307_at	0.000461	598.93	279.9	Rasgrp1	AF106070	NM_011246
378	93360_at	0.000466	1509.57	1005.43	Pmm1	AF007267	NM_013872
379	105205_at	0.000467	964.07	311.1	1110007A06Rik	AA467067	NM_024288
380	111628_at	0.000472	1339.67	758.63	D10Ertd516e	AA415523	XM_125901
381	117024_g_at	0.000473	1528.47	430.27	Alg2	AW121030	NM_019998
382	107784_at	0.00048	582.4	344.3	3830408P04Rik	AA790926	NM_023647
383	115657_at	0.000482	548.47	86.43	---	AA217038	NM_009784
384	138970_at	0.000482	5093.87	3884.2	B830017A01Rik	AW123948	XM_132047
385	104222_f_at	0.000486	571.5	231.6	Ggps1	C79210	NM_010282
386	112244_at	0.000487	353.8	182.33	1110018F06Rik	AI158684	XM_148904
387	168022_at	0.000489	1018.03	408.97	---	AV260075	---
388	99049_at	0.00049	566.43	362.37	Casp2	D28492	NM_007610
389	AFFX-TransRecMur/X57349_3_at	0.000493	359.8	134	Trfr	X57349	NM_011638
390	136666_at	0.000496	393.6	51.73	6330567E21Rik	AI848649	XM_357781
391	136535_at	0.000498	2545.47	1366.93	4930420O11Rik	AI642422	XM_283179
392	134758_at	0.000498	832.57	404.27	Hrb	AI666718	NM_010472
393	162527_s_at	0.000499	2123.5	1652.97	0610038L10Rik	AI848937	NM_019437
394	96191_at	0.0005	1979.7	1555.73	D130059B05Rik	AI852124	XM_129376
395	112350_at	0.000501	893.07	278.73	---	AA739089	XM_486359
396	165462_at	0.000509	5974.67	3526.87	Clcn2	AW048146	NM_133778
397	93881_i_at	0.000511	232.33	43.03	Tgoln1	D50032	NM_009443 /// NM_009444
398	92243_at	0.000512	1143.9	907.03	1810017N16Rik	AA117417	XM_356186
399	104557_at	0.000513	1372.63	796.4	Pitpnb	AI847097	NM_019640
400	94364_at	0.000519	1371.27	1032.6	Glg1	AI847926	NM_009149
401	110069_at	0.00052	1657.17	602.2	4930438D12Rik	AW123500	NM_175212
402	137360_at	0.000522	2134.03	1002.5	Pfc	AW123311	NM_007922
403	136206_at	0.000522	12953.4	6320.63	---	AI853974	XM_148399 /// XM_148683 /// XM_488776 /// XM_622736
404	102936_at	0.000523	1123.13	542.43	B4galt6	AW125314	NM_019737
405	108560_at	0.000524	4351.57	3112.8	---	AI849518	NM_026673

Table 5

406	163628_at	0.000528	1164.2	784.03	2810019K23Rik	AW124815	NM_027268
407	93806_at	0.000531	1185.23	904.67	Sh3bgrl	AI848671	NM_019989
408	115808_at	0.000531	1183.9	622.53	Ppm1a	AW046655	NM_008910
409	116963_at	0.000531	3139.9	1682.87	Freq	AW125370	NM_019681
410	163692_at	0.000534	1852.37	731.7	---	W84305	NM_133195
411	109020_at	0.000546	1391.97	911.8	Zfp216	AW122093	NM_009551
412	109475_at	0.000546	637.87	180.47	Dlgh2	AA250296	NM_011807
413	112282_s_at	0.000547	1412.7	721.27	Snx1	AI154073	NM_019727
414	160859_s_at	0.000549	557.4	257.67	Nfib	Y07685	NM_008687
415	117023_at	0.000552	991.37	497.17	Alg2	AW121030	NM_019998
416	166012_at	0.000558	4066.17	2857.57	Slc38a2	AV031649	NM_175121
417	117048_at	0.000564	3476.63	1922.9	0710001E13Rik	AI853636	NM_028755 /// NM_033264
418	110305_at	0.000565	948.27	606.3	Man1b	AA960561	NM_010763
419	134135_r_at	0.000572	2811.9	1356.43	Neurl	AI450910	NM_021360
420	166904_at	0.000573	2084.23	1139.27	2410012C07Rik	AW046085	NM_177261
421	114861_at	0.000574	480.17	62.67	9630005B12Rik	AI608153	NM_013862
422	109946_at	0.000578	12452.33	7446.67	Cds2	AW048308	NM_138651
423	165766_at	0.000581	4235.9	2303.57	MGC67646	AW121232	NM_198610
424	93056_g_at	0.000587	2771.13	1506.5	1110054N06Rik	AW049376	NM_175134
425	163507_at	0.000589	962.47	316.73	---	AW122375	NM_178615
426	94454_at	0.000591	1245.43	930.27	Dazap2	AF085348	NM_011873
427	138075_at	0.000591	6099.07	2946	Mapk9	AI852504	NM_016961 /// NM_207692
428	107900_at	0.000592	446.23	207.67	Erbb2ip	AW123554	NM_001005868 /// NM_021563
429	97998_at	0.000596	1196.5	428.73	Drpla	AC002397	NM_007881
430	101294_g_at	0.000597	326.03	248.57	---	Z84471	NM_008062 /// NM_019468
431	106250_at	0.000603	6352.23	2295.7	2310067G05Rik	AI851655	NM_025877
432	110753_at	0.000603	894.47	258.53	2700078E11Rik	AA763880	NM_030197
433	110191_at	0.000604	549.5	206.77	1110007A06Rik	AW125795	NM_024288
434	139232_at	0.000604	6386.77	4881.1	---	AI853452	NM_001005424
435	92763_at	0.000607	94.6	16.67	Abcb7	U43892	XM_356348
436	113425_at	0.000609	4291.87	1276.27	Ppp1r9a	AA986447	NM_181595
437	162520_at	0.000615	2740.3	1036.7	Tnfaip1	AI644149	NM_009395
438	136688_at	0.000616	1600.77	658.77	Ppm1l	AI853934	NM_178726
439	96607_at	0.000618	1537.97	951.07	1500003O03Rik	AW124902	NM_019769
440	92393_at	0.000618	312.67	104.27	Kcna3	M30441	NM_008418
441	133130_at	0.000619	1051.8	302.47	Scn3b	AW120594	NM_153522 /// NM_178227
442	94161_at	0.000627	1653.67	546.87	Prkce	AF028009	NM_011104
443	130290_at	0.000627	2324.93	1034.3	---	AW045806	XM_618813

Table 5

444	92946_f_at	0.00063	1884.43	1070.27	---	L32372	NM_013540
445	112835_at	0.000632	1733.27	1165.37	Cog4	AI840978	NM_133973
446	95138_at	0.000633	797.53	567.4	1110018O08Rik	AI836568	NM_178398
447	140490_at	0.000634	7291.1	1931.9	Pcsk2	AW120478	NM_008792
448	92449_at	0.000636	363.27	130.2	Gfra2	AF002701	NM_008115
449	AFFX-GapdhMur/M32599_5_at	0.000636	107421.83	71205.63	Gapd	M32599	NM_001001303 /// NM_001001978 /// NM_001029931 /// NM_008084 /// NM_199472 /// XM_139510 /// XM_204942 /// XM_356116 /// XM_356954 /// XM_483891 /// XM_484256 /// XM_484345 /// XM_484436 /// XM_484732 /// XM_485043 /// XM_485318 /// XM_485562 /// XM_485937 /// XM_486133 /// XM_486623 /// XM_486720 /// XM_487067 /// XM_618821 /// XM_619006 /// XM_619144 /// XM_619236 /// XM_619350 /// XM_619822 /// XM_619825 /// XM_619956 /// XM_619966 /// XM_620482 /// XM_620523 /// XM_620532 /// XM_621075 /// XR_000341
450	139220_at	0.000637	459.57	145.63	5730509K17Rik	AW046362	NM_172274
451	162862_at	0.000638	1541.07	982.93	1500004C10Rik	AW122442	NM_023824
452	106168_at	0.000639	8151.4	3139.7	Cplx2	AI848132	NM_009946
453	95924_at	0.00064	370.67	179.5	1700012B15Rik	AA473729	NM_028796
454	96211_at	0.000643	1611.37	948.27	Dpp8	AI846896	---
455	135242_at	0.000646	2448.87	317.17	---	AI839257	NM_174997
456	99515_at	0.000647	994.33	324.77	Ap2b1	AW046293	NM_027915
457	160766_at	0.000647	289.07	196.07	Cd2bp2	AA733868	NM_027353
458	101977_at	0.00065	6199.2	4347.4	Nudt3	AW121873	NM_019837
459	117036_at	0.000653	4438.63	2512.77	Dp1	AI849637	NM_007874
460	101419_at	0.000656	12958.4	8854.33	Tubb4	M28730	NM_009451
461	115771_at	0.000656	831.7	213.87	2210409H23Rik	AI930289	NM_175380
462	166303_i_at	0.000657	467.6	294	Wnt5a	AW045478	NM_009524
463	104503_at	0.000661	204.17	45.6	6030436C20Rik	AI563623	NM_178654
464	92433_at	0.000661	731.57	280.6	Kif5c	AF067180	NM_008449
465	99338_at	0.000661	498.7	255.63	D10Ertd516e	AA674798	XM_125901
466	107374_at	0.000663	915.13	585	2610002M06Rik	AW046865	---
467	112362_at	0.000667	1471.97	563.63	Sorl1	AI845170	NM_011436
468	164295_i_at	0.000667	2247.2	594.43	B230106I24Rik	AV231065	NM_178772
469	109368_at	0.00067	3723.7	2616.87	Elmo1	AI840476	NM_080288 /// NM_198093
470	162632_at	0.000674	811.93	557.27	4833405E05Rik	AA619039	NM_175353
471	136200_at	0.000675	1245.4	209.2	Tmod2	AI853421	NM_016711
472	138208_at	0.000677	1056.43	248.93	---	AW050216	NM_182995
473	110370_at	0.000681	488.5	140.87	Flrt3	AI447780	NM_178382
474	108538_at	0.000685	1832	1201.17	Ranbp2	AA726512	NM_011240
475	168159_at	0.00069	2856.9	2004.4	---	AI152637	---
476	138476_at	0.000691	5784.83	3483.73	Lass6	AI851865	NM_172856
477	97960_at	0.000693	1290.57	502.03	Usp22	AW125800	NM_001004143

Table 5

478	133885_at	0.000695	1392.07	539.97	---	AA168645	---
479	110457_at	0.000696	3201.57	1994.2	Hlf	AW123178	NM_172563
480	105624_at	0.000701	1393.67	618.63	0910001K20Rik	AA183352	NM_026719
481	163616_at	0.000702	744.6	337.2	1700012F10Rik	AI844628	NM_027946
482	167282_i_at	0.000703	6227.67	3854.03	Nxph1	AV342681	NM_008751
483	99014_at	0.000706	5986.5	4583.3	---	AI839886	NM_009685
484	111145_at	0.000706	826.6	310.53	4931426N11Rik	AW124601	NM_172579
485	117125_at	0.000707	1927.73	1228.63	Slc4a4	AI835705	NM_018760
486	110974_at	0.00071	503.17	281.23	B4galt6	AA881839	NM_019737
487	163536_at	0.000714	1046.63	325.27	3300002K07Rik	AI662303	NM_152809
488	138084_at	0.000715	6848.87	4102.53	---	AI840102	NM_001003824 /// NM_001003825 /// NM_001006668 /// NM_001006669 /// NM_001006674 /// NM_001006675 /// NM_001006676 /// NM_001006677 /// NM_001006678 /// NM_001006679 /// NM_001006680 /// NM_010611
489	94641_at	0.000717	335.73	188.7	A830016G23Rik	U69137	XM_283264
490	93976_at	0.000718	1774.9	1220.27	Cab39	AI836686	NM_133781
491	135927_at	0.00072	772.77	156.1	---	AW124923	NM_019931
492	101684_r_at	0.000723	728.13	353.5	---	X67863	NM_009276
493	95020_at	0.000725	2134.2	1373.4	9130415E20Rik	AI848868	NM_010581
494	97722_at	0.000725	558.1	418.3	Ssr1	AA879709	NM_025965
495	105411_at	0.000725	3974.53	2513.77	Myo5a	AI842846	---
496	160392_at	0.000728	721.43	440.7	B430110G05Rik	AW060358	NM_178696
497	140885_at	0.000735	14653.4	10832.13	---	AW121243	NM_001025074 /// NM_008745
498	169012_s_at	0.000735	2789.9	876.3	Camk2d	AV134810	NM_001025438 /// NM_001025439 /// NM_023813
499	111726_at	0.000739	635.27	303.33	Pcnx	AA797617	NM_018814
500	115798_at	0.00074	428.97	269.13	D330037H05Rik	AI048003	XM_128090
501	116147_at	0.000742	1397.23	598.7	Lin7c	AW125731	NM_011699
502	114608_at	0.000744	572.9	164.6	Thoc1	AA986864	NM_153552
503	114842_g_at	0.000746	2523.93	1668.97	Nf1	AA855356	NM_010897
504	105514_at	0.000746	549.93	317.73	E430023H19Rik	AW124739	NM_030131
505	92872_at	0.000747	4369.77	3575.73	1200016B17Rik	AI837715	NM_026267
506	111168_at	0.000748	289.93	48.9	6330500D04Rik	AA041998	NM_178658
507	110110_at	0.000749	1236.67	619.9	Ashl1	AI646464	NM_138679
508	94208_at	0.000755	1067.4	711.77	1700015E05Rik	AW045202	NM_027959
509	116576_at	0.000761	302.47	70.57	MGC38585	AI451563	NM_153538
510	98136_at	0.000762	951.43	551.5	Sms	AF031486	NM_009214
511	104282_at	0.000763	440.33	142.63	---	AW122808	---
512	113565_at	0.000767	6022.93	3241.87	1110063G11Rik	AW049089	NM_178874
513	94143_at	0.000771	448.8	148.43	Gfap	X02801	NM_010277

Table 5

514	95457_at	0.000774	2823.77	1775.3	1110001C20Rik	AI854214	NM_177730
515	161171_at	0.000778	369.33	236.17	---	AV226788	NM_008748
516	129017_at	0.000779	1884.93	855.13	---	AU017833	XM_354869
517	133499_at	0.000783	3039.43	1326.2	Whsc1	AI449553	XM_132006
518	115891_at	0.000785	1563.13	754.9	4930402H24Rik	AI481691	NM_029432
519	97198_at	0.000786	267.97	43.37	Abca1	X75926	NM_013454
520	92477_at	0.000787	1397.83	912.5	Spin	AA681862	NM_011462 /// NM_146043
521	108747_at	0.000789	792.27	384.4	---	AI553620	---
522	97471_at	0.000796	1545.17	1042.7	2310016N05Rik	AI848442	NM_028840
523	99035_at	0.000798	282	162.23	Pcyt1a	U84207	NM_009981
524	107774_at	0.0008	622.5	216.47	Tm4sf10	AI836428	NM_138751 /// NM_175771
525	117012_g_at	0.000802	2978.43	1095.03	Epb4.1l3	AW105743	NM_013813
526	110239_at	0.000804	472.13	162.67	2210402G22Rik	AW124610	NM_144516
527	110790_at	0.000806	1221.87	521.73	Gucy1a3	AW121879	NM_021896
528	117120_at	0.000806	1386.1	600	L3mbtl3	AW124145	NM_172787
529	116376_at	0.000807	5438.5	3051.73	BC003498	AI846073	NM_030263
530	138003_at	0.000808	2847.7	2076.07	Necl1	AI848148	NM_053199
531	105458_at	0.000809	747.53	506.77	9830132G07Rik	AI316857	NM_172643
532	99477_at	0.00081	416.83	156.77	Gng12	AI842738	NM_025278
533	129856_at	0.000814	5379.7	2278.77	Adcyap1r1	AW060198	NM_001025372 /// NM_007407
534	137565_at	0.000818	1581.87	803.6	---	AI482346	NM_025965
535	111105_at	0.000819	225.77	78.1	4921524P20Rik	AI050373	NM_026641
536	101966_s_at	0.00082	1303.43	549.13	Rnf13	AF037206	NM_011883
537	96580_at	0.000824	272.27	133.07	Pbx3	AF020199	NM_016768
538	114389_at	0.000827	6321.97	4552.2	Gabrb3	AI849425	NM_008071
539	168147_s_at	0.000831	4499.87	1120.2	Dcamkl1	AV209156	NM_019978
540	138466_at	0.000836	816.03	349.83	---	AI848373	---
541	99960_at	0.000838	1454.77	776.67	Map2k4	U18310	NM_009157
542	111405_at	0.00084	638.97	423.57	AI450344	AI847396	NM_178917
543	100113_s_at	0.000843	3385.73	2561.2	Kifap3	D50367	NM_010629
544	106953_i_at	0.000843	1034.37	686.73	G630013P12Rik	AW125203	XM_127501 /// XM_619147
545	94463_at	0.000844	1400.37	564.73	Clcn3	X78874	NM_007711 /// NM_173876
546	96273_at	0.000847	8334.53	4552.2	Nrgn	AI841709	NM_022029
547	98403_at	0.000848	1937	1304.53	Gna-rs1	X65026	NM_008136
548	115820_at	0.000848	2013.23	909.2	Nav1	AI852255	NM_173437
549	107956_at	0.000851	400.03	163.07	1700034P14Rik	AA675638	NM_028487
550	163540_i_at	0.000856	1807.33	887.23	4930438D12Rik	AA839266	NM_175212
551	113932_g_at	0.000863	1495.63	984.8	AA959742	AW230677	NM_133807

Table 5

552	117192_at	0.000868	403.47	104.67	2610204M12Rik	AW048378	NM_019426
553	166724_at	0.000869	2342.3	1496.2	Wwox	AI847565	NM_019573
554	103318_at	0.000872	288.53	188.37	Gabpb1	M74516	NM_010249 /// NM_207669
555	171396_at	0.000872	998.5	485.37	---	AV301383	NM_133752
556	111887_at	0.000874	2380.57	1899	Ube2j1	AA726802	NM_019586
557	99001_at	0.000877	478.13	210.07	Zfp292	AF017806	XM_620009
558	98905_at	0.000879	10004.8	6854	7-Sep	AJ223782	NM_009859
559	131856_at	0.000879	3022.17	1016.53	---	AW123974	---
560	133703_at	0.000881	1269.3	787.47	A030012M09Rik	AI462192	NM_183028
561	116564_at	0.000882	821.97	654.2	1500031A17Rik	AW125276	XM_130797
562	99800_at	0.000883	512.23	58.27	L1cam	X12875	NM_008478
563	93861_f_at	0.000886	552.03	283.53	---	M17327	NM_007799
564	114359_at	0.000888	1902.83	757.73	Mpv17l	AW049341	NM_033564
565	107399_at	0.000888	1267.3	577.47	9530039J15Rik	AW060961	NM_030138
566	104673_at	0.000889	902.73	370.67	Epha4	X65138	NM_007936
567	112159_at	0.00089	485.43	291.53	Stambp	AW044727	NM_024239
568	137045_at	0.00089	1313.5	582.9	Epb4.1l1	AI836271	NM_001003815 /// NM_001006664 /// NM_013510
569	138798_at	0.00089	1668.43	933.5	D10Ertd516e	AI644073	XM_125901
570	93664_at	0.000901	1123.93	404.47	Atp1b2	X16645	NM_013415
571	104373_at	0.000902	400.27	195.4	Aprin	AW046876	NM_175310
572	160603_at	0.000903	724.5	228.13	Pparbp	AF000294	NM_013634 /// NM_134027
573	110650_at	0.000903	3143.87	2539.2	Nrip1	AA959574	NM_173440
574	94719_at	0.000904	255.93	80.43	Kcna6	M96688	NM_013568
575	110202_at	0.000914	2861.73	1350.07	Zfp148	AA656577	NM_011749
576	101385_at	0.000916	2361.67	1761.73	Mbd3	AW047312	NM_013595
577	113908_at	0.000918	1342.83	1020.17	Alcam	AI853494	NM_009655
578	164227_at	0.000919	642.33	450.93	---	AV276161	XM_484601
579	112918_at	0.000924	4555.2	2967.33	LOC212285	AI842563	XM_132099
580	93212_at	0.000925	515.63	183.23	AW742319	Z97207	NM_021345
581	133141_at	0.000929	3076.83	1627.2	Slc25a16	AW122946	NM_175194
582	103264_at	0.000932	383.53	176.97	Mtmr1	AF073997	NM_016985
583	102305_at	0.000933	3379.73	2491.6	Gpr37l1	AB016602	NM_134438
584	111940_at	0.000934	3484.93	2434.2	8430423A01Rik	AW047744	NM_175294
585	97368_at	0.00094	1223.53	831.1	Akap1	U95145	NM_009648
586	95731_at	0.000943	1550.47	1172.47	Sesn1	AI843106	NM_001013370
587	104260_at	0.000944	1923.9	1600.63	---	AW123061	---
588	162961_at	0.00097	1672.13	950.63	1500005J14Rik	AI835531	NM_028058
589	160393_at	0.000979	1678.7	1153.37	4930555L11Rik	AI853226	XM_284250

Table 5

590	95785_s_at	0.000982	1932.3	968.77	---	Y13361	NM_009005
591	115435_at	0.000982	2594.03	1476.3	Bcr	AW125149	XM_125706
592	102573_at	0.000985	584.83	223.1	---	U56651	NM_008751
593	114481_at	0.000986	372.57	108.97	Agps	AI007022	NM_172666
594	135813_at	0.000986	1624.73	1185.17	A830091N21Rik	AI848290	NM_146140
595	112961_at	0.000993	120.37	16.7	4733401N12Rik	AI256641	NM_001013391
596	116126_at	0.000994	970.1	300.23	Npnt	AA682063	NM_001029836 /// NM_033525
597	107877_at	0.000995	340.9	120.43	Sacm1l	AW125412	NM_030692
598	160480_at	0.001009	3507.7	2098.7	Ptprs	X82288	NM_011218
599	115469_at	0.001009	1122.83	400.97	E030026I10Rik	AI836780	NM_008687
600	166535_r_at	0.001009	6843	3033.13	1700020I14Rik	AA718150	XM_488956
601	96333_g_at	0.00101	1405.23	911.77	Snx2	AW259199	NM_026386
602	138963_r_at	0.001013	5011.7	1696.57	---	AI846642	---
603	138402_at	0.001013	2417	848.83	---	AW123197	NM_177907 /// NM_178906
604	105107_at	0.001015	3651.2	2367.57	C330018B01	AW121339	NM_172948
605	134241_at	0.001016	700.27	374.13	C330039G02Rik	AA656737	NM_172699
606	131020_at	0.001022	3587.33	2383.53	Ap3b2	AW121779	NM_021492
607	93634_at	0.001023	1541.1	809.6	Fbxw1b	AW125157	NM_134015
608	92426_at	0.001024	889.27	658.67	Tm4sf9	AI877157	NM_019571
609	93921_at	0.001024	1640.67	845.23	Bat3	AI573601	NM_057171
610	171206_f_at	0.001024	3738.83	2893.2	---	AV145515	XM_134542
611	112245_at	0.001027	356.03	135.8	---	AW122302	XM_355205
612	160117_at	0.001029	3476.2	1603.27	Tef	AI850638	NM_017376 /// NM_153484
613	93164_at	0.001031	172.6	22.87	Rnf2	Y12783	NM_011277
614	103746_at	0.001033	257.63	61.63	D11Ertd530e	AA797843	NM_199196
615	134345_at	0.001034	1016	732.37	---	AI586144	---
616	100566_at	0.001035	2136.9	969.9	Igfbp5	L12447	NM_010518
617	116164_at	0.001035	815.73	493.2	Pde4a	AW045844	NM_019798 /// NM_183408
618	167421_at	0.001035	4889.7	2278.87	Enpp5	AI852186	NM_032003
619	95135_at	0.001038	2205.93	1710.27	3110038L01Rik	AI844396	NM_026524
620	115916_at	0.001043	679.5	272.43	Rasa2	AA691429	NM_053268
621	160640_at	0.001044	830.97	690.17	Galnt11	AW121625	NM_144908
622	113046_at	0.001049	1900.33	267.83	---	AI842091	NM_009443 /// NM_009444
623	96144_at	0.001056	952.53	509.6	Idb4	AJ001972	NM_031166
624	162708_at	0.001057	1926.63	1120.43	Tceb2	AI558072	NM_175229
625	115537_at	0.001069	478.77	316.1	1700023F20Rik	AW045284	NM_172618
626	AFFX-MURINE_b1_at	0.001074	186123.4	125937.83	---	U01310	NM_021286 /// NM_021411 /// NM_023651 /// NM_028150 /// NM_146176 /// XM_484087 /// XM_622223

Table 5

627	162832_at	0.001077	9066.33	6335.2	Kif1b	AI839711	NM_008441 /// NM_207682
628	168528_f_at	0.001077	5410.6	2575.47	1500010B24Rik	AV296073	NM_025437
629	135765_at	0.00108	2427.4	1517.93	4932409F11Rik	AI853231	NM_029404
630	163700_at	0.001081	410.37	131.4	Fbxl5	AI846617	NM_178729
631	167934_at	0.001086	518.2	157.67	AI836376	AV263372	NM_178896
632	109601_at	0.001087	555.53	326.1	AI447711	AI592241	NM_207214
633	98491_at	0.001088	1307.53	754.03	2610313E07Rik	AI286904	NM_026011
634	94197_at	0.001089	444.97	164.5	Ugcg	D89866	NM_011673
635	93055_at	0.00109	3257.87	1715.17	1110054N06Rik	AW049376	NM_175134
636	98349_at	0.001097	273.33	167.73	Il6st	X62646	NM_010560
637	162628_at	0.001102	1446.3	886.07	2610040E16Rik	AA863780	NM_024194
638	131137_at	0.001102	488.03	173	---	AU024549	---
639	116096_at	0.001111	703.9	298.53	C630029K18Rik	AA718043	NM_144871
640	162709_at	0.001111	263.67	58.17	1810031K17Rik	AA760414	NM_026977
641	163129_at	0.001111	586.6	328.13	2410002O22Rik	AA501071	NM_025879
642	130531_at	0.001111	1788.67	505.77	4933434E20Rik	AI851476	NM_025762 /// NM_027500
643	108016_at	0.001113	2321.23	1322.2	C230096C10Rik	AI841508	NM_146157
644	108502_at	0.001119	1418.2	674.23	Trio	AI605420	XM_619309
645	93529_at	0.00112	2158.43	1031.13	D8Wsu49e	AW125219	NM_028007
646	129464_at	0.001122	1162.47	444.8	Tdrd3	AW228955	NM_172605
647	113593_at	0.001123	690.23	345.7	Add3	AI839335	NM_013758
648	94001_at	0.001124	641.53	353.67	Elavl1	U65735	NM_010485
649	168123_at	0.001127	19705	6449.67	6330407J23Rik	AI849309	NM_026138
650	104940_at	0.00113	526.23	312.53	---	AI465338	XM_355332
651	110709_at	0.001135	207.67	152.4	Pank1	AA619470	NM_023792
652	112682_at	0.001145	815.73	283.33	Kif1b	AW060517	NM_008441 /// NM_207682
653	101357_at	0.001146	1422.2	977.13	Ap2a1	X14971	NM_007458
654	94155_at	0.001146	1233.93	469.63	Rgs4	AB004315	NM_009062
655	106573_at	0.001149	2024.83	1638.9	---	AW122342	NM_133741
656	95286_at	0.001154	5758.03	4361.4	Clu	D14077	NM_013492
657	104704_at	0.001159	1400.23	984.93	Clcn4-2	AI837630	NM_011334
658	92827_at	0.001161	114.93	26.63	Nsdl	AF064553	NM_008739
659	98490_at	0.001166	720.7	329.2	2610313E07Rik	AA822412	NM_026011
660	109491_at	0.001169	900.7	589.17	BC003322	AA759948	NM_030257
661	108507_at	0.00117	2846.17	1439.07	Hectd1	AI837295	XM_354671
662	95507_at	0.001171	2603.57	2071.3	Prps1	AB025048	NM_021463
663	111568_at	0.001172	214.1	167.33	---	AI875666	XM_128508
664	166335_at	0.001173	379.8	202.57	4930451A13Rik	AA793889	NM_026254

Table 5

665	104375_at	0.001178	12466.07	6747.1	Spock2	AI844853	NM_052994
666	111796_at	0.001189	4365.1	2363.87	Mbnl2	AW123074	NM_175341 /// NM_207515
667	112040_at	0.001189	969.27	478.57	Gabra4	AI606317	NM_010251
668	97259_at	0.001192	2678.53	1686.23	AW559096	AJ005983	NM_021548
669	111956_at	0.001205	681.67	397.33	Ggps1	AA647683	NM_010282
670	93005_at	0.001213	8868.2	2576.07	Syt1	D37792	NM_009306
671	116956_at	0.001213	528.43	192.27	Kctd12	AI848366	NM_177715
672	93007_at	0.001216	375.8	196.73	Npy1r	Z18280	NM_010934
673	130418_f_at	0.001227	6848.73	3431.53	---	AU018327	---
674	93350_f_at	0.001235	452.7	307.93	Zfp422	AW209414	NM_026057
675	92507_at	0.001237	335.4	124.6	Utrn	Y12229	NM_011682
676	93422_at	0.001239	297.6	187.63	Pftk1	U62391	NM_011074
677	112965_at	0.001241	173.03	49.67	4933439F18Rik	AI842014	NM_025757
678	168126_s_at	0.001248	2003.03	1180.8	---	AI987839	NM_011811
679	93666_at	0.001249	530.7	262.27	Lmo2	M64360	NM_008505
680	103624_at	0.001258	769.03	365.5	2900073H19Rik	AW121323	NM_026615
681	133906_at	0.001258	2252.8	702.73	C78339	AI482265	XM_127312
682	162746_at	0.001259	2335.73	1752.8	---	AW046094	NM_133766
683	115917_at	0.00126	786	527.4	Man1b	AA874421	NM_010763
684	AFFX-CreX-3_st	0.001267	2045.07	688.63	---	X03453	---
685	93922_g_at	0.001269	1357.1	876.7	Bat3	AI573601	NM_057171
686	129305_at	0.001271	1618.73	750.2	Icam1	AI846658	NM_203507
687	117147_at	0.001273	3576.97	2528.97	Ssbp3	AI840440	NM_023672 /// NM_198438
688	102893_at	0.001274	330.6	134.3	Pou2f1	X68363	NM_011137 /// NM_198932 /// NM_198933 /// NM_198934
689	102741_at	0.001276	203.83	54.57	Adar	AW046250	NM_019655
690	115476_at	0.00128	2033.07	1491.07	---	AI851690	---
691	115904_at	0.001283	865.07	601.1	1110065L07Rik	AI788994	XM_133990
692	141105_s_at	0.001286	1344.33	553.57	4.93E+26	AI850917	NM_177858
693	99068_at	0.001289	451.13	341.77	Mcpr	X80169	NM_008569
694	97313_at	0.00129	9359.57	7678.6	Gdi1	U07950	NM_010273
695	160413_at	0.001293	4668.03	2649.77	Nsg2	U17259	NM_008741
696	106886_at	0.001294	123.8	39.07	---	AW048254	XM_484197
697	116746_at	0.001296	10539.87	7665.2	DAP-3	AI850878	NM_198618
698	92292_at	0.001303	811.7	381.27	Slc2a3	M75135	NM_011401
699	165602_f_at	0.001307	6007.57	4189.07	D430025H09Rik	AW050057	NM_145616
700	107033_at	0.00131	5452.53	2829.53	5830434P21Rik	AW047040	NM_172661
701	132815_at	0.001316	1415.63	559.1	Sec61a2	AI006571	NM_021305
702	139538_at	0.001326	1249.2	975.97	E130318E12Rik	AI481680	NM_145510

Table 5

703	92863_at	0.001327	7466.33	4378.43	Wbp2	U40826	NM_016852
704	112324_at	0.001328	396.3	146.93	Bap1	AW122786	NM_027088
705	165724_at	0.001331	9488.83	6396.9	4930438D12Rik	AW045382	NM_175212
706	116121_at	0.001332	382.53	118.8	3110040D16Rik	AA793572	XM_126172
707	129025_at	0.001336	837.57	199.53	Atrn	AA543234	NM_009730
708	139171_at	0.001336	4104.27	1804.2	Gpr88	AI841541	NM_022427
709	114560_at	0.001337	817.23	306	9130022A11Rik	AA692431	NM_172677
710	136081_at	0.001345	433.1	101.27	BC025474	AA688667	NM_172473
711	128590_at	0.001347	916.83	124.9	4631416I11Rik	AW121649	NM_001003909
712	109995_at	0.001349	2684.47	1685.03	C920003I06	AI850852	NM_001013380
713	160830_at	0.00135	2674.03	1886.03	Cnil	AB006191	NM_009920
714	99577_at	0.001356	862.03	563.57	Kitl	M57647	NM_013598
715	114523_at	0.001361	748.77	345.63	A630007B06Rik	AA265784	NM_170757
716	100557_g_at	0.00137	1791.77	1265.23	2310046H11Rik	AW121930	NM_145625
717	98818_at	0.001373	343.97	42.9	Nr3c1	X04435	NM_008173
718	94506_at	0.001376	290.53	186.63	---	AI853113	NM_026623
719	99380_at	0.001381	502.13	97.57	Kcna2	M30440	NM_008417
720	102556_at	0.001382	184.5	39.37	---	M99377	NM_007417
721	102296_at	0.001393	3879.83	2626.2	Pcsk2	M55669	NM_008792
722	112830_at	0.001403	305.6	60.73	2810457I06Rik	AI847602	NM_176860
723	112906_at	0.001407	1169.9	707.43	Rala	AA833038	NM_019491
724	103475_s_at	0.001424	263.5	48.4	Ate1	AF079096	NM_001029895 /// NM_013799
725	98894_at	0.001426	346.63	161	2610016F04Rik	AA867655	XM_619217
726	134010_s_at	0.001431	1333.2	616.87	4930565N16Rik	AI451887	XM_125517
727	116691_at	0.001436	7501.63	4627.8	Adcy1	AW123151	NM_009622
728	164118_at	0.00144	422.73	186.3	Foxp2	AA616089	NM_053242 /// NM_212435
729	166197_at	0.00144	4054.3	1708.47	---	AV266520	NM_017381
730	140329_at	0.001441	426.67	182.8	C730034D20Rik	AA563183	NM_144814
731	113450_at	0.001445	795.3	465.2	Lix1	AA982628	NM_025681
732	132437_s_at	0.001445	7220.33	4246.83	Anapc5	AA986796	NM_021505
733	98925_at	0.001453	3160.43	984.57	Vamp2	U60150	NM_009497
734	113699_at	0.001455	704.93	304.37	Purb	AW123681	NM_011221
735	100560_at	0.001456	4420.47	3097.43	Pafah1b1	U95116	NM_013625
736	93722_at	0.001459	554.9	352.03	Ensa	AJ005985	NM_001026212 /// NM_019561
737	95404_at	0.001466	2715.4	1262.07	Pafah1b2	AW123453	NM_008775
738	109125_at	0.001479	821.7	235.8	2310036D22Rik	AI789000	NM_027992
739	116379_at	0.00148	657.5	342	2310035C23Rik	AA178683	NM_173187
740	96560_at	0.001482	583.13	370.3	Myo6	AA648027	NM_008662

Table 5

741	116425_at	0.001483	3913.93	2116.03	Ntrk2	AW125471	NM_001025074 /// NM_008745
742	101456_at	0.001501	1558.77	799	Zfp106	AF060245	NM_011743
743	112389_at	0.001503	3261.37	2203.47	Vapb	AI842621	NM_019806
744	167062_at	0.001503	1538.2	1160.47	2900026A02Rik	AI158998	NM_172884
745	93326_at	0.001504	20792.93	11486.77	Tm4sf2	D26483	NM_019634
746	138004_at	0.001504	682.27	528.33	AW492253	AI849156	NM_183142
747	163773_at	0.001507	2447.1	1057.97	Napg	AI450216	XM_355095
748	104612_g_at	0.00151	786.63	560.93	Wdr26	AI854008	---
749	102698_at	0.001517	523.77	189.37	Epas1	AF045160	NM_010137
750	97935_at	0.001521	1290.1	826.67	4121402D02Rik	AI842970	NM_028722
751	103957_at	0.001523	290	87.5	Trfr	X57349	NM_011638
752	106917_at	0.001527	1391.23	1082.17	C530030I18	AI836095	NM_207255
753	103070_at	0.001539	2755.27	1890.97	Ptpns1	AB018194	NM_007547
754	92448_s_at	0.001543	856.63	482.2	Gfra2	AF079107	NM_008115
755	92802_s_at	0.001548	12974.27	5003.73	Plp	M16472	NM_011123
756	138139_at	0.001552	2293.03	1017.23	---	AW046476	XM_488712
757	166855_at	0.001557	370.2	78.47	B230382K22Rik	AI843969	---
758	106847_at	0.001558	1562.37	558.13	9330157P13Rik	AI842383	NM_001003829 /// NM_177049
759	114222_at	0.001559	1146.13	195.53	D130026O08Rik	AW122396	NM_080448 /// NM_153070
760	97559_at	0.001561	7491.37	5688.13	Eef2	M76131	NM_007907
761	112973_at	0.001564	454.5	192.73	D14Ertd436e	AA920081	NM_172599
762	98504_at	0.001574	1502.7	523.27	Rock2	U58513	NM_009072
763	104125_at	0.001575	503	274.6	AL022832	AA763673	NM_011276
764	96634_at	0.001579	742.37	533.6	5730469M10Rik	AI850090	NM_027464
765	114712_at	0.001583	8919.5	3938.4	Mef2c	AI132554	NM_025282
766	115120_at	0.001585	769.33	435.03	---	AA123427	NM_028136
767	108264_at	0.001587	565.77	172.2	---	AW125497	---
768	97284_at	0.001589	938.03	817.1	Bcl2l13	AI853789	NM_153516
769	160921_at	0.001592	476.5	392.17	Acas2l	AW125884	NM_080575
770	113234_at	0.001594	504.67	293.67	1600022A19Rik	AA674083	NM_146062 /// NM_175363
771	95324_at	0.0016	1373.07	692.8	Atp2b2	AF053471	NM_009723
772	115356_s_at	0.001602	227.27	126.97	Bmpr1a	AI663515	NM_009758
773	111172_at	0.001602	1389.3	743.17	D1Ertd622e	AI987691	NM_133825
774	97263_s_at	0.001603	2443.07	1293.97	Csnk1d	AI846289	NM_027874 /// NM_139059
775	109607_at	0.001603	1004.93	503.1	Pdcl	AW108059	NM_026176
776	100954_at	0.001606	269.7	222.63	Hrb	AF057287	NM_010472
777	115140_at	0.001609	16646.8	12223.53	BC028881	AW124719	NM_183315
778	97114_at	0.001611	10846.03	6729.07	Psap	U57999	NM_011179

Table 5

779	112722_at	0.001622	1057.4	459.17	D6Ertd253e	AW124381	NM_178608
780	106605_at	0.001623	791.67	230.53	B230106I24Rik	AW045971	NM_178772
781	93087_r_at	0.001626	663.57	480.17	Igk-V8	AA267185	NM_013918
782	137614_at	0.001626	2302.33	1635.17	Zfp369	AI507190	NM_178364
783	166773_at	0.001627	586.8	154.6	E430019N21Rik	AA426869	NM_001024604
784	96193_at	0.001628	1263.7	819.03	Dm9	Z38011	NM_010058
785	100307_at	0.001634	1804.3	555.83	Lyl1	AA002843	NM_010906
786	100933_at	0.00164	6969.67	3641.97	Stx1a	D45208	NM_016801
787	130532_at	0.001644	2457.53	1540.7	Sox11	AI836553	NM_009234
788	107811_at	0.00165	412.7	112.17	AI663987	AA237472	NM_033526
789	138395_at	0.00165	3773.93	2003	---	AW121944	---
790	101370_at	0.001659	982.5	352.47	Kpna1	U20619	NM_008465
791	117176_at	0.001676	5944.5	3670.6	Ank2	AI846530	NM_001034168 /// NM_178655
792	92801_at	0.001677	5462.87	2599.47	Plp	M37335	NM_011123
793	133140_at	0.001677	4864.5	1561.3	Dnm	AW121936	NM_010065
794	169344_r_at	0.001681	958.37	427.33	1200009O22Rik	AV007963	NM_025817
795	99834_at	0.001684	135.67	76.57	Nrg3	AF010130	NM_008734
796	134260_at	0.001686	2718.03	1402.37	---	AI549876	---
797	105883_at	0.001688	1209.8	585.53	Kif3a	AW124694	---
798	109064_at	0.00169	512.8	237.8	5830451P18Rik	AI616202	XM_619244
799	117267_at	0.001701	411.6	161.2	2310044G17Rik	AI853744	NM_173735
800	114734_at	0.001703	2529.2	1392.97	B230106I24Rik	AW012646	NM_178772
801	106857_at	0.001703	685.97	103.33	Pcdh9	AW048370	XM_139187
802	107753_at	0.001703	812.47	267.73	Etohi2	AW045353	NM_026799
803	138087_at	0.001719	7629.63	5413.77	---	AI843229	NM_010199 /// NM_183064
804	116436_at	0.00172	844.37	567.17	6330501D17	AI180937	XM_127854
805	104467_at	0.001722	598.17	387.93	Cpd	AA763004	NM_007754
806	163933_at	0.001722	799.97	402.9	Pten	AI616079	NM_008960
807	106249_at	0.001725	1167.63	180.33	---	AI048542	NM_025877
808	105896_at	0.001727	755.73	256.3	Cdk8	AI854046	NM_145155
809	104685_g_at	0.001736	762.33	311.83	---	AI847120	NM_008169
810	95431_at	0.001737	728.4	339.8	D16Wsu109e	AA623426	NM_138599
811	92513_at	0.001745	1052.27	673.13	Stag2	AJ002636	NM_021465
812	113199_at	0.001746	8243.57	6451.2	Rab15	AW123563	NM_134050
813	164134_at	0.001746	3892.1	2857.5	D030041I09Rik	AI843915	NM_175460
814	113766_at	0.001749	3935.8	3299.33	Abi2	AI854004	NM_198127
815	161054_at	0.001751	2230.3	1637.37	Spock1	X92864	NM_009262

Table 5

816	110507_at	0.001757	1301.63	546.6	AU067726	AW121504	NM_177762
817	95139_at	0.001765	506.93	339.73	1110018O08Rik	AW122075	NM_178398
818	97211_at	0.00177	1534.13	1248.2	3230401N03Rik	AI747444	NM_026139
819	114641_at	0.001775	5713.93	3911.1	1500001H12Rik	AW120690	NM_021316
820	111713_at	0.001775	1857.6	760.27	5730405I09Rik	AA839183	NM_026484
821	160181_at	0.001803	3382.17	1712.33	Syp	X95818	NM_009305
822	94564_at	0.001808	2183.1	1615.53	Sult4a1	AF059257	NM_013873
823	135691_at	0.001815	673.63	418.4	1300018L09Rik	AA882067	---
824	116112_at	0.001816	305	164.33	Igf1r	AI854325	---
825	160806_at	0.001824	669.73	429.57	---	AF099988	NM_016866
826	107874_at	0.001826	921.13	490.53	B230380D07Rik	AI848418	NM_172772
827	95613_at	0.001829	3323.13	2054.9	Cox7a2	AW122573	NM_133718
828	93958_at	0.001833	1701.73	1022.7	Rnf14	AA086863	NM_020012
829	99038_at	0.001834	1717.3	1266.37	Adss2	L24554	NM_007422
830	130840_at	0.001835	929.4	438.63	9330164H19Rik	AI413355	NM_178704
831	139173_at	0.001842	2767.47	1473.63	Ap3b2	AI838160	NM_021492
832	104270_at	0.001843	787.43	338.47	Adrbk1	AA982714	NM_130863
833	139200_at	0.001843	1560.93	910.97	---	AW045408	---
834	97130_at	0.001852	226.73	69.7	Ate1	AF079097	NM_001029895 /// NM_013799
835	94003_at	0.001853	1722	886	Prkwnk1	AI848510	NM_198703
836	108996_at	0.001858	891.67	557.47	BC030477	AI840999	NM_177618
837	129304_at	0.001858	568.03	271.7	Sall1	AA386439	NM_021390
838	101865_at	0.001861	386.7	197.8	Pip5k2a	AB009615	NM_008845
839	95888_at	0.001863	118.93	21.93	Laf4l	AI507266	NM_033565
840	116241_at	0.001872	1297.57	878.7	---	AA137949	---
841	168497_at	0.00188	8847.37	2666.73	Spin.	AA921202	NM_011462 /// NM_146043
842	94766_at	0.001888	23137.27	16004.73	Eef1a1	M17878	NM_010106
843	129028_at	0.001893	6683.4	2789.83	---	AU021802	XM_139187
844	100887_at	0.001894	296.37	192.9	Smc6l1	AI838562	NM_025695
845	92287_at	0.001898	1095.7	554.37	Socs5	AF033187	NM_019654
846	104108_at	0.001902	2098.53	1649.97	Rab6ip1	AJ245569	NM_021494
847	109545_at	0.001902	885.23	649.5	AI314180	AW123771	NM_172381
848	138458_at	0.001902	7611	6138.93	Kcna1	AW049444	NM_010595
849	137709_at	0.001909	2601.77	1519.9	Pnma2	AW047936	NM_175498
850	92857_at	0.001911	727.4	423.43	Rpl22	AI853960	NM_009079
851	167474_at	0.001918	690.83	314.33	Trim23	AV316037	NM_030731
852	134131_at	0.001921	1702.4	790.03	9030425C21Rik	AI154671	NM_026343
853	97823_g_at	0.001922	867.27	660.53	Pak2	AW122689	NM_177326

Table 5

854	92995_at	0.001922	17564.13	9488.1	Vsnl1	D21165	NM_012038
855	115070_at	0.001922	2892.73	1859.2	---	AA711252	NM_009700
856	138969_at	0.00193	2792.77	884.33	Trim37	AI852231	NM_197987
857	113069_at	0.001937	419.87	185.3	5730589K01Rik	AA162011	NM_023434
858	168332_f_at	0.00194	9447.57	4641.37	Spop	AV353779	NM_025287
859	160786_f_at	0.001944	690.23	364.93	Actr1b	AI843424	NM_146107
860	92465_at	0.00195	489.83	222	Plcb1	U85713	NM_019677
861	104364_at	0.001958	528.73	429.43	Mapkapk5	AF039840	NM_010765
862	137130_at	0.001961	3177.5	2447.4	A430106J12Rik	AI662755	NM_176841
863	114829_at	0.001969	2036.33	1179.3	Tln2	AI851526	XM_486227
864	140484_at	0.00197	286.87	97.7	Dhx29	AW121071	NM_172594
865	129311_at	0.001977	4804	2612.17	Lin7c	AU022293	NM_011699
866	110604_at	0.00198	882.23	414.33	6820402O20Rik	AW121207	XM_133187
867	163686_at	0.001981	155.57	118.9	Rnf38	AA833486	NM_175201
868	114639_at	0.001983	453.07	254.23	5031439A09Rik	AI317333	NM_026582
869	167174_at	0.001984	530.63	243.4	Prps2	AV115966	NM_026662
870	99178_at	0.001986	3013.7	2157.8	Gpm6b	AI845652	NM_023122
871	100529_at	0.001994	1341.37	491.13	Ube2h	U19854	NM_009459
872	104681_at	0.002011	771.4	496.77	Diap1	U96963	NM_007858
873	112462_at	0.002012	1109.1	425.33	Hipk3	AI153524	NM_010434
874	108465_at	0.002012	939.2	482.9	2610200G18Rik	AI835135	NM_025998
875	113055_at	0.002012	2365.37	1284.8	Acvrinp1	AA275788	NM_015823
876	107592_at	0.002016	1425.6	860.43	6330415F13Rik	AI841656	NM_027533
877	96126_at	0.002023	365.4	228.57	Sgpl1	AF036894	NM_009163
878	AFFX-PyruCarbMur/L09192_MB_at	0.002025	1210.3	687	Pcx	L09192	NM_008797
879	131386_at	0.002048	1318.47	661.47	Stoml1	AI849419	NM_026942
880	99494_at	0.002063	8132.57	6541.67	Serpini1	AJ001700	NM_009250
881	160265_at	0.002067	1480.03	1154.7	Eif5	AW123979	NM_173363
882	112854_s_at	0.00207	1474.03	664.53	D17Wsu92e	AW123169	XM_128587
883	102827_at	0.002077	1361.93	1016.13	Nek7	AW124633	NM_021605
884	135082_at	0.002079	376.27	98.13	A630025O09Rik	AW229335	NM_172637
885	168513_f_at	0.002083	1592.43	1138.7	Rnut1	AV331209	NM_178374
886	111125_at	0.002084	3718.73	2158.73	Spred1	AI391368	NM_033524
887	107830_at	0.002085	2145.13	647.13	Spred1	AI390404	NM_033524
888	116955_at	0.002089	3206.03	1201.3	---	AI847605	NM_213616
889	112851_at	0.002096	4093.27	1882.47	0710001E19Rik	AI852174	NM_029716 /// NM_175752
890	139230_at	0.00211	3510.87	591.2	2610102M01Rik	AI836575	NM_030203
891	109747_at	0.002112	1821.3	1207.63	---	AW046149	NM_147153 /// NM_178851

Table 5

892	106980_at	0.002113	1346.53	880.5	Pvrl1	AI847001	NM_021424
893	116432_at	0.00212	1093.7	405.43	Epb4.1l2	AI845744	NM_013511
894	106977_at	0.002121	5761.47	4343.47	---	AI839553	XM_622404
895	97560_at	0.002145	1110.43	384.17	---	AF037437	NM_011179
896	135230_at	0.002145	468.1	166.07	Tmem10	AI835050	NM_153520
897	96188_at	0.002147	611.2	237.97	Adar	AF052506	NM_019655
898	93083_at	0.002157	1684.73	1553.07	Anxa5	D63423	NM_009673
899	112716_at	0.002175	968.33	686.1	B4galt6	AW122682	NM_019737
900	160954_at	0.002189	3256.63	1179.8	Syn2	AF096867	NM_013681
901	108004_at	0.002195	3912.8	3015.93	2310036D22Rik	AI787353	NM_027992
902	135257_at	0.002195	6328.97	3062.4	A430106J12Rik	AI848406	NM_176841
903	116612_at	0.002202	2946.17	2434.6	4930541M15Rik	AI854230	XM_129477
904	160714_at	0.002211	337.73	234.07	Gab1	AI046826	NM_021356
905	102922_at	0.00222	695.23	505.5	1110020B03Rik	AI851387	NM_145823
906	136725_at	0.00222	5690	3726.47	---	AI849504	---
907	100153_at	0.002224	2306.97	1673.4	Ncam1	X15052	NM_010875
908	92727_at	0.002225	1503.2	1170.37	Apba2	L34676	NM_007461
909	164022_i_at	0.002225	1975.87	154.4	6330404M18Rik	AW123985	XM_132762
910	116250_at	0.002236	307.33	198.03	D6Bwg1452e	AA111217	XM_143984
911	98540_g_at	0.002252	573.77	272.47	Cops2	AF071312	NM_009939
912	139180_at	0.002257	1790.17	872.47	4930565F05Rik	AI847792	NM_029947
913	115796_at	0.00227	332.4	192.43	Cul5	AA647303	NM_027807
914	168387_i_at	0.002271	1499.07	1184.17	2610034K17Rik	AW228984	XM_135805
915	135358_s_at	0.002272	85628.3	45757.8	---	AW211972	NM_015770
916	129925_at	0.002272	4057.23	1385.67	---	AW212719	NM_146239
917	106131_at	0.002278	2433.8	1414.47	Rnf44	AI854545	NM_134064
918	116072_at	0.002287	1231	765.53	Stard4	AI853043	NM_133774
919	110241_at	0.002287	420.5	94	2210402G22Rik	AW049195	NM_144516
920	108912_at	0.002287	1697.9	734	Pde2a	AW048257	NM_001008548
921	105908_at	0.002288	800.2	533.47	Rasa2	AW122748	NM_053268
922	AFFX-GapdhMur/M32599_3_at	0.002289	82984.83	62397.77	Gapd	M32599	NM_001001303 /// NM_001001978 /// NM_001029931 /// NM_008084 /// NM_199472 /// XM_139510 /// XM_354601 /// XM_356092 /// XM_356116 /// XM_483891 /// XM_483995 /// XM_484256 /// XM_484307 /// XM_484345 /// XM_484436 /// XM_484482 /// XM_484654 /// XM_484732 /// XM_484834 /// XM_485043 /// XM_485318 /// XM_485562 /// XM_485937 /// XM_486133 /// XM_486264 /// XM_486386 /// XM_486623 /// XM_486720 /// XM_486749 /// XM_487067 /// XM_489580 /// XM_618821 /// XM_619136 /// XM_619142 /// XM_619236 /// XM_619350 /// XM_619393 /// XM_619956 /// XM_619966 /// XM_620176 /// XM_620348 /// XM_620482 /// XM_620523 /// XM_620532 /// XM_620646 /// XM_621075 /// XM_621114 /// XM_622431 /// XR_000341 /// XR_000357
923	100388_at	0.00229	576.3	325.87	Gnao	L34216	NM_010308

Table 5

924	136232_at	0.002297	2482.27	1011.3	Dock3	AI840717	NM_153413
925	100707_at	0.002301	260.7	119.67	Sh3md2	AF030131	NM_021506 /// NM_198678
926	105835_at	0.002301	2920.97	2394.93	2410018I08Rik	AI852059	NM_177561
927	136732_at	0.002308	1367.37	884.4	Tdrkh	AI850904	XM_131021
928	114602_at	0.002319	372.8	307.67	5730596K20Rik	AW228836	---
929	164142_at	0.002332	3658.37	1938.3	Syt13	AI844411	NM_030725
930	166667_r_at	0.002339	1498.47	1253.7	Arl6ip2	AV334690	NM_019717 /// NM_178050
931	95803_at	0.002349	923.5	383.73	Ptpns1	D85785	NM_007547
932	116557_at	0.002349	1401.33	1147.87	D5Wsu178e	AI853125	NM_027652
933	163501_at	0.002351	780.67	670.97	Dctn4	AI840620	NM_026302
934	93859_at	0.002357	578.13	320.03	Mtif2	AI875598	NM_133767
935	96252_at	0.002359	1077.23	736.53	Pdcd6ip	AJ005073	NM_011052
936	104005_at	0.002359	1767.93	1109.87	B4galt2	AB019541	NM_017377
937	116203_at	0.00236	1546.6	1025.83	Mtmr1	AA959458	NM_016985
938	164020_at	0.00236	473.8	258.2	---	AW061143	NM_133766
939	105507_at	0.002366	1147.7	577.8	---	AI642321	NM_201531
940	101148_at	0.002377	247.03	114.2	Prkcl	D28577	NM_008857
941	113027_at	0.002383	585.23	332.57	6330441O12Rik	AA816040	XM_284697 /// XM_359343
942	105086_at	0.002383	649.6	359.77	---	AI648838	NM_026623
943	101430_at	0.002396	703.47	342.53	Sox4	AW124153	NM_009238
944	167597_at	0.002409	9070.87	5186.03	---	AW123917	XM_622756
945	116311_at	0.002413	1528.9	650.47	Ivns1abp	AA673812	NM_028582 /// NM_054102
946	92288_at	0.002415	192.17	57.83	Ap1g1	X54424	NM_009677
947	115233_at	0.002416	1966.83	1188.83	Map3k10	AA498142	XM_194344
948	112402_at	0.002417	1200.53	1012.7	BC037112	AW045953	XM_132015
949	93831_at	0.002422	200.97	98.23	Nono	AI316087	NM_023144
950	111644_at	0.002428	370.53	240.8	Ap3s2	AW050091	NM_009682
951	93892_at	0.00243	589.33	266.4	Cugbp2	Y18298	NM_010160
952	93909_f_at	0.002433	2164.33	831.57	---	X04120	NM_009834 /// XM_620701
953	117250_at	0.002448	2794.97	1696.87	B930006L02Rik	AW121519	NM_178764
954	114841_at	0.002459	730.17	300.17	Nf1	AA855356	NM_010897
955	98332_at	0.002468	2511.27	1398.87	Kcnj9	U11860	NM_008429
956	129113_at	0.002483	779.67	427.33	1700030B17Rik	AV283721	NM_027407
957	109909_at	0.002494	1302.4	648.6	Wdr22	AW124614	NM_177267
958	129906_at	0.002508	3073.73	1592.3	Prkaa2	AA960412	NM_178143
959	115640_at	0.002514	815.87	388.3	1700020I14Rik	AI451541	XM_488956
960	139035_at	0.002515	514.87	182.27	---	AI846518	NM_011638
961	103369_at	0.002519	742.67	377	---	AW049142	XM_489146

Table 5

962	98863_at	0.002521	196.93	59.1	Grik2	X66117	NM_010349
963	110208_at	0.002524	1504.83	944	Strn4	AA727401	NM_133789
964	101834_at	0.002528	536.93	296.7	Mapk3	Z14249	NM_011952
965	115236_at	0.002538	824.9	551.77	Usp15	AA824120	NM_027604
966	99662_at	0.00254	310.93	252.8	Pcnt2	AI194767	NM_001002929
967	111948_at	0.002547	1390.7	907.47	Insig2	AW048761	NM_133748 /// NM_178082
968	105577_g_at	0.002547	1210.07	457.8	---	AA467595	---
969	100970_at	0.002548	1469.97	1011.03	Akt1	X65687	NM_009652
970	114782_at	0.00255	3392.7	1986.5	Arhn	AI841945	NM_009708
971	92280_at	0.002563	323.53	104.63	Strm	AA867778	NM_134156
972	105610_at	0.002563	499.87	265.73	1110020B03Rik	AA388982	NM_145823
973	160681_at	0.002568	223.2	108.4	Papola	AI131735	NM_011112
974	163248_at	0.002574	3939.27	2807.5	---	AI847753	NM_009784
975	101034_at	0.002575	1198.2	563.67	Grb2	U07617	NM_008163
976	140489_f_at	0.002587	761.9	279.6	1500012D09Rik	AW060560	NM_172601
977	166212_i_at	0.002591	747.8	485.73	---	AA275007	---
978	96115_at	0.002594	4581.1	2694.67	Dp1	U28168	NM_007874
979	113093_at	0.002603	868.6	406.67	AW743433	AV337617	NM_172649
980	113575_at	0.002608	398.53	251.2	3732409C05Rik	AI931943	NM_026143 /// NM_027379
981	96936_at	0.00261	1218.07	960.73	Copg	AI020792	NM_017477 /// NM_201244
982	163090_at	0.002626	799.37	492.3	---	AA755748	XM_130163
983	135090_at	0.00264	2548.77	1200.6	---	AA172354	NM_138679
984	97195_at	0.002643	734.2	331.83	Gnai1	U38501	NM_010305
985	109007_at	0.002644	549.1	287.03	3010001K23Rik	AA738680	NM_028223
986	105981_at	0.002651	399.8	103.3	Qk	AW125862	NM_021881
987	114117_f_at	0.002664	4813.73	3809.7	---	AW061131	XM_283816 /// XM_485113 /// XM_485115 /// XM_485123 /// XM_485126 /// XM_619853 /// XM_619854 /// XM_619855 /// XM_619856 /// XM_619857
988	97489_at	0.002667	483.93	394.57	Pygb	AI846739	NM_153781
989	116161_at	0.002668	290.67	195.8	Msi2h	AI430099	NM_054043
990	103543_at	0.002669	2257.93	1509.8	---	AW208098	XM_132255
991	103800_at	0.002679	1182.53	899	Abcc5	AB019003	NM_013790 /// NM_176839
992	168255_at	0.002688	1293.47	675.27	4933428A15Rik	AV280494	NM_027756
993	105431_at	0.002692	844.87	452.47	2810442O16Rik	AW211998	NM_024196
994	108760_at	0.002694	110.63	58.5	4732479N06Rik	AW061034	NM_172540
995	136065_at	0.002718	304.47	157.87	---	AI465326	---
996	112414_at	0.002725	583.83	242.83	Pank3	AA673475	NM_145962
997	114056_at	0.002726	191.2	91.43	C530047H08Rik	AA982455	XM_619423
998	117239_at	0.002729	769.87	314.8	Slc6a8	AW125428	NM_133987

Table 5

999	101305_at	0.00273	658.07	249.17	---	M88299	NM_008900
1000	105718_at	0.00273	721.47	390.97	Pldn	AW125039	NM_019788
1001	167383_f_at	0.002764	755.03	436.3	0610041E09Rik	AV300355	NM_025335
1002	105825_at	0.002765	1436.5	740.2	Scn8a	AI850246	NM_011323
1003	116843_at	0.002777	3378.5	2058.53	Fads2	AW045920	NM_019699
1004	100951_at	0.002783	387.2	200.1	Pkd2	AF014010	NM_008861
1005	94619_at	0.002796	875.73	444.83	Grid1	D10171	NM_008166
1006	100093_at	0.002799	2894.03	2255.83	Pctk1	X69025	NM_011049
1007	95446_at	0.002809	1364.5	1299.97	6330577E15Rik	AW120502	NM_026377
1008	168114_i_at	0.002817	15782.03	12659.3	Syt4	AW121878	NM_009308
1009	93460_at	0.002819	91.7	55.3	Acvrl	L15436	NM_007394
1010	107367_at	0.002822	876.07	477.17	5830411G16Rik	AW045967	XM_132538
1011	107274_at	0.002825	535.4	330.23	1110018N15Rik	AI842625	NM_146153
1012	109662_at	0.002844	755.37	219.27	1500010B24Rik	AW122695	NM_025437
1013	98946_at	0.002848	758.73	532.73	2700038M07Rik	AF033186	NM_019653
1014	115015_at	0.002853	1926.4	1242.47	Atp11b	AI852900	NM_029570
1015	112182_at	0.002858	3521.03	2493.67	---	AI847095	NM_020270
1016	104611_at	0.002861	642.47	333.97	Wdr26	AI854008	---
1017	166819_at	0.002874	4231.9	3104.43	Pcsk2	AI839700	NM_008792
1018	130649_at	0.002877	2949.37	1810.67	2610002M06Rik	AW011755	---
1019	99465_at	0.002879	1193.9	632.17	Mecp2	AJ132922	NM_010788
1020	133686_at	0.002883	484.6	176.03	6030460N08Rik	AI451399	XM_127084
1021	166531_at	0.00289	965.1	315.43	Fem1b	AI843581	NM_010193
1022	97544_at	0.0029	8606.87	6450.9	Ywhaz	D83037	NM_011740
1023	108889_at	0.002914	390.03	174.93	AW547365	AA870215	NM_133891
1024	114398_at	0.002916	738.3	448.2	0610041E09Rik	AA267114	NM_025335
1025	116982_at	0.002916	497.13	200.3	2610030H06Rik	AI840175	---
1026	108070_s_at	0.002917	2618.4	1474.1	A930006D20Rik	AW124994	XM_358889 /// XM_489610
1027	96351_at	0.002921	1101.07	623.63	---	AI846097	NM_027453
1028	162538_at	0.002922	3060.37	1823.23	Nptxr	AI841230	NM_028763
1029	163457_f_at	0.002931	533.17	304.97	Slit3	AI605218	XM_203363
1030	162853_r_at	0.002934	753.1	326.9	5730406M06Rik	AI838332	XM_283936
1031	112844_at	0.00294	1324.83	802.9	Dst	AI843343	NM_010081 /// NM_133833 /// NM_134448
1032	106087_at	0.002948	1784.93	811.07	---	AI851254	NM_028821
1033	102928_at	0.00296	2365.6	2069.8	Hdh	L28827	NM_010414
1034	94449_at	0.002968	5425.9	3390.3	Pcdhga12	AI854522	NM_033574 /// NM_033575 /// NM_033576 /// NM_033577 /// NM_033578 /// NM_033579 /// NM_033580 /// NM_033581 /// NM_033582 /// NM_033583 /// NM_033584 /// NM_033585 ///

Table 5

							NM_033586 /// NM_033587 /// NM_033588 /// NM_033589 /// NM_033590 /// NM_033591 /// NM_033592 /// NM_033593 /// NM_033594 /// NM_033595
1035	113005_at	0.00297	1528.97	1279.43	A730024F05Rik	AA967534	---
1036	97462_at	0.002974	1134.3	667.5	3110006P09Rik	AI847584	NM_026521
1037	92629_f_at	0.002982	5398.17	4574.13	Hdgf	D63707	NM_008231
1038	129282_at	0.002992	18654	8595.4	Tm4sf9	AW124518	NM_019571
1039	134511_at	0:002997	762.87	192.2	Cpeb4	AI851572	NM_026252
1040	163474_at	0.002998	2666.37	1280	Socs5	AA967794	NM_019654
1041	93632_g_at	0.00301	1234.1	645.9	Lbcl1	X95761	NM_008487
1042	140704_at	0.003012	2837.8	2120.47	Rdgb2	AW120913	NM_011256
1043	112103_at	0.003013	651.93	376.43	Narg1	AA795513	NM_053089
1044	164183_at	0.003014	222	130.17	1110033M05Rik	AA432497	XM_193728
1045	162740_at	0.003018	1918.17	1251.33	Btbd2	AW047954	XM_354550
1046	105826_at	0.00302	2897.27	1666.57	Cntn1	AI843096	NM_007727
1047	92938_at	0.003053	1922.4	876.4	Gabra1	X61430	NM_010250
1048	100751_at	0.003058	278.73	158.93	Adam10	AF011379	NM_007399
1049	110578_at	0.003077	317.33	199.23	Taf3	AA176054	NM_027748
1050	97463_g_at	0.003086	2864	1713.1	3110006P09Rik	AI847584	NM_026521
1051	97220_at	0.00309	333.57	280.7	Dscr2	AW122732	NM_019537
1052	108375_at	0.003092	660.2	400.77	AI645720	AA982346	NM_173784
1053	166266_i_at	0.003097	883.2	635.03	Sec63	AI592740	---
1054	113110_at	0.003113	545.2	386.67	---	AA960405	NM_011721
1055	136188_at	0.003125	4176.97	1143.8	C630035N08Rik	AI852133	NM_175427
1056	109785_at	0.003126	8380.17	4921.97	Pip5k1c	AW123736	NM_008844
1057	164801_at	0.003132	2338.8	1853.03	---	AV291488	NM_025283
1058	116943_at	0.00314	633.23	552.43	AW547186	AI852450	NM_177592
1059	116834_at	0.003141	2022.93	1039.37	9030612M13Rik	AI840710	NM_172458
1060	111547_at	0.003143	628.8	411.13	Prkab2	AI851666	NM_182997
1061	165449_f_at	0.003148	3556.43	1701.3	Ube2j1	AI848527	NM_019586
1062	165615_at	0.003155	1568.53	1153.67	A430031N04	AI850732	NM_177718
1063	167515_at	0.003159	517.73	375.13	Orc31	AV229483	NM_015824
1064	92312_at	0.003162	123.4	67.6	Pik3c2a	U55772	NM_011083
1065	161119_at	0.003192	327.3	248.73	Epha5	AI854630	NM_007937
1066	112838_at	0.0032	2452.03	1899.37	Fa2h	AW125159	NM_178086
1067	136210_at	0.003223	4633.07	2440.57	App	AI854555	XM_488788
1068	110829_at	0.003242	2793.73	1885.07	Syt13	AI842207	NM_030725
1069	106113_at	0.003244	418.4	199.5	---	AI850393	---
1070	160189_at	0.003253	1862.07	909.33	4933436C10Rik	AI843747	NM_027722

Table 5

1071	115102_at	0.003259	588.67	490.8	AI987944	AW060550	NM_183167
1072	116898_at	0.003275	2754.27	1884.47	Pip5k2b	AI845380	NM_054051
1073	96570_at	0.003285	76.2	40.17	BC027756	AV381276	NM_145991
1074	112376_at	0.003287	940.13	276.27	D15Ertd412e	AW124163	NM_134094
1075	109656_at	0.003291	695.3	187	2210417C17Rik	AW123915	XM_129809
1076	94985_at	0.003298	301.13	203.5	Syncrip	AI846392	NM_019666 /// NM_019796
1077	133139_at	0.003301	13123.6	7463.67	---	AW122295	NM_009062
1078	111720_at	0.003303	2293.27	819.2	Tnnt1	AW124387	NM_172894
1079	114550_at	0.003315	958.03	530.07	LOC212285	AA718110	XM_132099
1080	164230_at	0.003325	620.17	410.7	Eprs	AV211782	XM_129647
1081	111855_at	0.003326	2697.13	2160.17	2310003F20Rik	AI843117	NM_001003719 /// NM_019994
1082	162819_at	0.003326	2576	1559.67	Mlc1	AI843987	NM_133241
1083	93762_at	0.00333	3707.67	2009.27	Ppp2r4	AI841493	NM_138748
1084	111263_at	0.00334	3269	2375.8	Rbm9	AI840760	NM_053104 /// NM_175387
1085	107304_at	0.003345	618.27	374.73	Pcdh7	AW047051	NM_018764
1086	101946_at	0.003355	268.27	132.33	Lypla1	AA840463	NM_008866
1087	111173_at	0.003355	1130.13	574.1	C330002I19Rik	AW122339	XM_126866
1088	103569_at	0.003362	432.57	188.3	---	AI842874	NM_019464
1089	106200_at	0.003363	4572	3430.13	E030034P13Rik	AI842120	NM_153791
1090	114686_at	0.003381	1562.5	1059.63	C330007P06Rik	AW048693	XM_135837
1091	103924_at	0.003385	1521.03	1154.3	D8Ertd319e	AW048884	NM_026792
1092	116107_at	0.003396	552.87	209.57	Son	AI854469	NM_019973 /// NM_178880
1093	167524_at	0.003403	773.13	132.53	1810011E08Rik	AI593305	---
1094	99144_s_at	0.003416	667.77	254.97	Tgoln1	D50031	NM_009443
1095	162987_at	0.003417	18536.97	11628.67	Kif5a	AW120637	NM_008447
1096	166622_at	0.003422	2114.9	816.47	B930052A04Rik	AI835355	NM_177193
1097	165580_i_at	0.003424	2336	1588.53	Kirrel3	AI847076	---
1098	133809_at	0.003428	1905.17	715.3	4732418C07Rik	AA914736	NM_172698
1099	106089_at	0.003445	219.17	90.9	C330005L02Rik	AI851303	NM_138756
1100	94243_at	0.003446	1413.1	1058.67	4930432B04Rik	AI849588	NM_029437
1101	94009_at	0.003447	1799.5	1280.4	2610301I15Rik	AI848888	NM_026456
1102	163269_at	0.003475	210.93	107.07	Smc1l1	AI875533	NM_019710
1103	138138_at	0.003476	5836.5	4296.2	---	AW046406	NM_010600
1104	163863_at	0.00348	600.1	299.53	4933406P09Rik	AI596813	---
1105	116709_at	0.003484	611.03	500.23	---	AW122414	NM_011990
1106	163646_at	0.003487	343.8	223.57	Jam2	AI853724	NM_023844
1107	110964_at	0.003506	5769.3	4336.27	Pde2a	AW120981	NM_001008548
1108	92580_at	0.003511	778.53	395.67	Hars	U39473	NM_008214

Table 5

1109	141033_at	0.003514	806.97	390.33	---	AI594656	---
1110	98460_at	0.003523	2056.8	1590.97	Fto	AJ237917	NM_011936
1111	114996_at	0.003535	243.73	93.5	2810417D08Rik	AA967301	NM_027421
1112	92611_at	0.003539	1135.17	759.2	Gpiap1	U18773	NM_016739
1113	92974_at	0.003554	139.27	89.5	Zfp37	X52533	NM_009554
1114	106819_at	0.003561	382.8	210.03	---	AW061288	---
1115	AFFX-BioC-5_at	0.003571	5733.7	3070.47	---	J04423	---
1116	107389_at	0.003577	1146.97	667.07	---	AW049675	NM_011531 /// NM_177129
1117	139237_r_at	0.003587	8019.93	5350.47	Dscr1l1	AW046916	NM_030598 /// NM_207649
1118	108048_at	0.003595	1954.07	1225.73	A630084M22Rik	AI836268	NM_177305
1119	160676_at	0.003597	2059	1627	C330018J07Rik	AI839212	---
1120	111480_at	0.003602	9835.5	6031.27	---	AI847025	NM_020270
1121	116917_at	0.003608	1015.97	605.07	LOC279653	AI843367	XM_205287
1122	116672_at	0.003615	443.77	171.47	Osbpl8	AA611861	NM_001003717 /// NM_175489
1123	109335_at	0.003617	2410.03	1330	9430023P16Rik	AI840418	NM_001005507
1124	100051_at	0.00365	1567.4	1072.43	Epb7.2	U17297	NM_013515
1125	92467_g_at	0.003656	822.93	346.6	Plcb1	U85714	NM_019677
1126	160819_at	0.003666	19645.87	16520.9	Ndr4	AW121600	NM_145602
1127	105420_at	0.003673	212.37	102.47	Rab14	AI649155	NM_026697
1128	137084_at	0.00368	2412.4	1590.37	4930565N16Rik	AA624105	XM_125517
1129	98027_at	0.003684	629.23	512.07	Col9a2	Z22923	NM_007741
1130	139426_r_at	0.003697	1330.53	861.53	---	AW228933	NM_010206
1131	98386_s_at	0.003698	676.83	497.1	Cacna1c	U17869	NM_009781
1132	94064_at	0.0037	489.77	297.9	Zfp91	U05343	---
1133	138986_at	0.003711	7325.8	4388.13	Centg3	AI847278	NM_139153
1134	163530_at	0.003716	2447.73	1764.13	---	AW121535	---
1135	114409_at	0.003717	988.9	100.23	Nktr	AA655805	NM_010918
1136	117137_at	0.003719	7803.5	4906.87	Camk2g	AW121347	NM_178597
1137	138182_at	0.003722	1410.33	991.1	9630036L12Rik	AW049816	XM_288123
1138	94488_at	0.003737	789.97	626.27	1110059P08Rik	AI847041	NM_025418
1139	139029_at	0.003746	585	158	---	AI845271	---
1140	112427_at	0.003752	476.73	150.7	AI427653	AI854077	NM_178714
1141	111156_at	0.003753	118.27	16.73	Jmy	AA666916	NM_021310
1142	167250_s_at	0.003762	514.6	294.57	Lactb2	AV052394	NM_145381
1143	138381_at	0.003768	1611	902.2	---	AW060967	---
1144	167783_f_at	0.003769	3583.93	1394.87	1810009A16Rik	AV262024	XM_355528
1145	98993_at	0.003776	3752.03	3061.53	Ppp2r5c	U59418	NM_012023
1146	100155_at	0.003791	1018.63	762.03	Ddr1	L57509	NM_007584

Table 5

1147	97554_at	0.003806	829.8	615.73	BC005624	AI838889	NM_144885
1148	99804_at	0.003831	724.53	464.33	---	M97516	NM_007418
1149	93590_at	0.003844	453.97	300.93	Ndst1	AI844370	NM_008306
1150	103029_at	0.003864	1570.27	1138.3	Pdcd4	D86344	NM_011050
1151	98150_at	0.003875	3189.33	2476.53	Rab11b	L26528	NM_008997
1152	101927_at	0.003894	4972.6	3027.8	Prkar1b	M20473	NM_008923
1153	135253_at	0.003899	6231.53	4823.53	---	AI847615	---
1154	106967_at	0.003901	95.23	26.67	Cul4b	AI427169	NM_028288
1155	139980_g_at	0.003905	1746.5	862.57	Ndufs1	AI450646	NM_145518
1156	168462_at	0.003907	1684.07	1102.9	---	AV340874	XM_139540
1157	131255_at	0.003924	1788.63	836.17	C630016B22Rik	C88213	NM_172051
1158	139519_at	0.003924	19113.3	9458.93	Gabra2	AW046395	NM_008066
1159	102151_at	0.003925	892.83	474.43	---	L10084	NM_007419
1160	107766_at	0.003927	461.67	267.87	6330500A18Rik	AI426461	NM_172675
1161	111782_at	0.00393	1880.23	1330.47	2310065H12Rik	AW122149	NM_029648
1162	109511_at	0.003933	456.67	234.33	Cyld	AA798616	NM_173369
1163	112948_at	0.003939	16916.9	13046	D9Bwg0185e	AI844254	NM_173781
1164	111006_at	0.003964	7360.23	5591.4	Plcb1	AI131739	NM_019677
1165	117011_at	0.003965	1769	797.2	Epb4.1l3	AW105743	NM_013813
1166	139278_at	0.003975	5870.17	2669.23	BC042620	AW049028	XM_128530
1167	102664_at	0.003977	789.07	324.1	Cdk5r	U89527	NM_009871
1168	92341_at	0.003977	1049.17	426.87	B3galt2	AF029791	NM_020025
1169	163988_at	0.003978	342.93	188.03	2410127E18Rik	AW125271	NM_029742
1170	138036_at	0.003986	3275.4	1463.77	---	AI851444	---
1171	97865_g_at	0.003994	1788.17	1212.83	2510049I19Rik	AW258842	NM_026455
1172	102402_at	0.004	1547.33	1161.43	Gbas	AJ001261	NM_008095
1173	97904_at	0.004014	5447.03	4117.3	Actr3	AW123953	NM_023735
1174	103428_at	0.004014	636.87	502.4	Pold3	AW049684	NM_133692
1175	140889_s_at	0.004014	6993.13	3471.67	---	AW122377	XM_488870
1176	99882_at	0.004021	388.63	92.27	Ids	L07921	NM_010498
1177	115814_at	0.004029	1912.73	882.87	2210417C17Rik	AI047908	XM_129809
1178	138946_at	0.00404	4868.67	1548.07	Syt7	AI844346	NM_018801 /// NM_173067 /// NM_173068
1179	160417_at	0.004041	853.17	360	Kif5b	U86090	NM_008448
1180	141051_at	0.004041	488.97	281.37	Fgf10	AI527654	NM_008002
1181	103766_at	0.004044	138.63	77.83	Sema5a	X97817	NM_009154
1182	109945_at	0.004057	4654.53	3402.2	D130026O08Rik	AI850918	NM_080448 /// NM_153070
1183	114518_at	0.004061	765.73	513.23	Ppm1a	AA254205	NM_008910
1184	99077_at	0.004075	365.17	294.63	Thra	X07750	NM_178060

Table 5

1185	99440_at	0.004079	799.53	377.3	Nfib	Y07686	NM_008687
1186	93463_at	0.004086	439.07	223.8	Usp19	AW122517	NM_027804
1187	136193_i_at	0.004107	1759.83	1134.73	Cul2	AI852917	NM_029402
1188	106484_at	0.004109	135.73	35.57	---	AI846694	NM_029804
1189	111832_at	0.004116	1564.73	975.87	---	AA930337	NM_172827
1190	100507_at	0.004125	2430.17	1695.13	Nov	Y09257	NM_010930
1191	111409_at	0.00413	582.83	400.3	---	AI835528	NM_029654
1192	112049_at	0.004134	206.23	69.13	Ncoa2	AW121738	NM_008678
1193	97944_f_at	0.004142	705.77	475.23	---	AF099808	NM_177288 /// XM_619247
1194	160686_at	0.004175	666.67	505.93	5730555F13Rik	AI836015	NM_025690 /// NM_026337
1195	138554_at	0.004176	1472.43	914.57	---	AI853109	XM_484423
1196	94435_at	0.004186	976.33	503.53	D10Ertd438e	AI839117	---
1197	162910_at	0.004186	516.27	375.5	Xpot	AI851617	XM_125902
1198	129310_at	0.004189	671.13	133.37	---	AA638581	XM_109700 /// XM_489741
1199	167028_at	0.004189	1734.03	1332.5	Fads3	AI841650	NM_021890
1200	110172_at	0.004197	1010.8	790.7	4930444A02Rik	AA929827	NM_029037
1201	93606_s_at	0.004198	1773.03	1081.3	Igsf4	AB021966	NM_001025600 /// NM_018770 /// NM_207675 /// NM_207676
1202	116355_at	0.0042	640.77	531.5	Mllt7	AA840142	---
1203	164257_at	0.004222	241.57	55.83	5430432P15Rik	AI462502	XM_129246
1204	93712_at	0.004231	499.33	298.33	Ccnt1	AF095640	NM_009833
1205	109397_at	0.004232	1682.07	1284.67	E2f4	AI844030	NM_148952
1206	96959_at	0.004236	2696.6	1909.67	Ube2n	AW210080	NM_080560
1207	104625_at	0.004238	641.17	407.37	---	AA874130	NM_011847
1208	160363_at	0.00424	1135.07	932.97	Tcfl1	D43643	NM_009336
1209	100413_at	0.004251	972.7	699.6	Zap3	AB033168	NM_178363
1210	103667_at	0.004272	598.03	477.93	---	AA866655	---
1211	97227_at	0.004284	331.87	157.7	Gnal2	M63659	NM_010302
1212	133128_at	0.00429	5006.57	2000.7	8430419L09Rik	AW120461	NM_028982
1213	171126_f_at	0.004292	2937.53	2239.87	---	AV050312	NM_145465
1214	104475_at	0.004293	516.7	339.93	---	AW124101	---
1215	109521_at	0.004301	1484.37	1240.57	---	AW123386	NM_008957
1216	103228_at	0.004303	853.93	459.87	Mtmr7	AF073882	NM_019433
1217	137563_f_at	0.004303	544.03	276.9	Akap7	AA966954	NM_018747
1218	114383_at	0.004309	649.33	450.67	Sc5d	AI834900	NM_172769
1219	102225_at	0.004313	1407.33	1042.07	9630005B12Rik	AA163268	NM_013862
1220	163749_at	0.004316	958.63	457.2	1200007B05Rik	AA433491	NM_026165
1221	106571_at	0.00432	511	336.53	Lztfl1	AI849674	NM_033322
1222	107880_at	0.004333	1459.67	958.07	---	AI846611	NM_030719

Table 5

1223	94362_at	0.004352	1169.87	1068.53	Nras	AI843682	NM_010937
1224	96801_at	0.004367	1742.87	1264.73	Ak1	AJ010108	NM_021515
1225	103710_at	0.004379	146.47	126.8	---	AI037032	NM_001029892
1226	167468_at	0.004382	579.43	394.67	AW011752	AV322674	NM_134034
1227	134046_at	0.00439	858.6	312.87	Wnt5a	AA288297	NM_009524
1228	117107_at	0.004392	4034.33	2874.17	Ppm1l	AI837768	NM_178726
1229	104216_at	0.004395	250.13	126.7	Shoc2	AF068921	NM_019658
1230	140886_at	0.004401	1988.5	1330.13	E130307J04Rik	AW121467	NM_021885
1231	101830_at	0.004423	383.2	281.57	Ryr3	X83934	XM_619795 /// XM_619796
1232	116003_at	0.004424	696.9	438.97	Slc35e3	AI594591	NM_029875
1233	93063_at	0.004462	23246.1	15966	App	U82624	NM_007471
1234	93616_g_at	0.004464	269.13	202.03	Pbx3	AF020200	NM_016768
1235	97210_at	0.004478	1133.07	893.2	1700037H04Rik	AW048446	NM_026091
1236	111753_at	0.00448	1066.4	520.9	Zfp294	AI156159	XM_128374 /// XM_489597
1237	105838_at	0.004486	1454.6	1290.33	Ppp2r5b	AI846204	NM_198168
1238	163041_at	0.004491	16587.2	11789.37	D10Ertd749e	AI846333	NM_025635
1239	136007_at	0.004509	2482.17	1049.2	BC044798	AW122183	NM_172442
1240	101889_s_at	0.004522	486.63	179.73	Rora	U53228	NM_013646
1241	131220_f_at	0.004529	8316	6792.17	4931426N11Rik	AW123699	NM_172579
1242	94196_at	0.004537	399.2	286.37	Ikbkg	AF069542	NM_010547 /// NM_178590
1243	99036_s_at	0.004542	176.03	58.5	Map2k7	AB005654	NM_011944
1244	115855_at	0.004571	566	206.93	Man2a2	AI851620	NM_172903
1245	108554_at	0.004578	2974.77	1457.53	4631427C17Rik	AI851845	NM_021414
1246	136202_at	0.004608	1048.97	392.87	Usp33	AI853456	NM_133247
1247	168228_i_at	0.004617	598.77	208.63	Slc35a5	AV260137	NM_028756
1248	163425_at	0.004623	900.03	501.43	1500012D09Rik	AA472312	NM_172601
1249	108044_at	0.00463	456.4	242.5	2310007F12Rik	AW123980	NM_175146
1250	99048_g_at	0.004632	2054.9	724.07	Mobp	U81317	NM_008614
1251	103559_at	0.004647	3027.67	1508.97	Prkaca	M12303	NM_008854
1252	AFFX-BioC-3_at	0.004654	1293	561.17	---	J04423	---
1253	114015_at	0.004659	1213.93	651.73	Leprotl1	AW122473	NM_026609
1254	139533_at	0.004667	1847.6	670.97	6820402O20Rik	AW047575	XM_133187
1255	138058_at	0.004684	1572.47	1103.27	Disp2	AI835296	NM_170593
1256	109951_at	0.004686	459.8	305.13	---	AI644184	NM_199476
1257	94918_at	0.004691	1078.17	957.2	Aars	AI839392	NM_146217
1258	110421_at	0.004698	648.03	425.3	0610010K06Rik	AW060214	NM_027861
1259	95416_at	0.004731	557.03	323.93	Usp15	AI642184	NM_027604
1260	105934_at	0.004731	263.1	81.03	9130423L19Rik	AI846379	NM_029869 /// NM_133906

Table 5

1261	105901_at	0.004741	4201.7	3196.97	Neurod2	AI849563	NM_010895
1262	105272_at	0.004744	452.37	262.27	4930487N19Rik	AA139112	XM_283206
1263	96854_at	0.004748	2550.2	1889.2	Copa	AJ010391	NM_009938
1264	109962_at	0.004763	1268.53	571.63	Prkar2b	AI314322	NM_011158
1265	103682_at	0.004767	301.47	185.2	C80913	AA122571	NM_011274
1266	93540_at	0.00477	2499.67	2067.37	Adprh	L13290	NM_007414
1267	112053_at	0.004784	600.67	334.83	E130103E02Rik	AI451118	XM_150227
1268	160558_at	0.004822	1258.3	1084.3	Akt2	U22445	NM_007434
1269	113753_at	0.004831	571.8	206.3	Stard4	AA895787	NM_133774
1270	98587_at	0.004833	1673.8	956.17	Nap1l1	X61449	NM_015781
1271	106023_at	0.004833	503.97	353.9	Dph2l2	AW047512	NM_026344
1272	93839_at	0.004837	7516.33	4968.97	Rtn3	AI854888	NM_001003930 /// NM_001003933 /// NM_001003934 /// NM_053076
1273	139261_at	0.004839	5346.13	3049.13	D6Ertd32e	AW046224	NM_001003955 /// NM_177466
1274	108362_g_at	0.004841	2428.9	806.77	Nr3c1	AW060548	NM_008173
1275	99855_at	0.004847	617.43	456.8	Map3k5	AB006787	NM_008580
1276	99045_at	0.004853	7833.93	6114.47	Eno2	AC002397	NM_013509
1277	115740_at	0.00487	244.87	113.67	2610020C11Rik	AI875624	NM_028130
1278	163130_at	0.004895	6232.4	4534.37	---	AW212010	NM_007561
1279	99046_at	0.004916	1178.2	523.73	Mobp	AI834776	NM_008614
1280	104105_at	0.004933	1530.77	1265.5	Xpo6	AI854665	NM_028816
1281	96433_at	0.004944	92.8	44.37	---	AA673236	NM_021323
1282	160428_at	0.004952	636.53	356.63	Suclg2	AF058956	NM_011507
1283	137719_at	0.004957	1227.03	282.53	Csmd3	AW049014	XM_139502
1284	160427_at	0.004963	1807.47	1393.1	---	AW046323	NM_178610
1285	108712_at	0.004975	1985.57	1585.03	Cobl	AI844390	NM_172496
1286	115718_at	0.004986	239.9	123	D630032B01Rik	AW049329	NM_172532
1287	139199_at	0.004988	1465.7	684.6	Slc12a6	AI847794	NM_133648 /// NM_133649
1288	129880_s_at	0.004988	11640.43	8627.07	Bhlhb5	AW122356	NM_021560
1289	160240_at	0.004991	2287.57	1901.53	1110003E01Rik	AI852051	NM_133697
1290	99047_at	0.005009	3848.47	1793.43	Mobp	U81317	NM_008614
1291	98007_at	0.005013	987.23	808.07	Rps6ka2	AJ131021	NM_011299
1292	95559_at	0.00502	2954.2	2562.97	6330403K07Rik	AI838836	NM_134022
1293	92397_at	0.005024	2527	1814.8	Centg2	AW123016	NM_178119
1294	104119_at	0.005027	796.67	593	AW060714	AI845028	NM_146084
1295	101571_g_at	0.005034	849.5	561.93	Igfbp4	X76066	NM_010517
1296	113014_at	0.005036	119.73	59.53	Sfmbt1	AA882264	NM_019460
1297	138126_at	0.005039	1710.6	817.43	---	AW048176	XM_354566

Table 5

1298	105243_at	0.00506	856.17	480.97	D6Ertd349e	AI557996	NM_182784
1299	96066_s_at	0.005073	13711.33	10007.77	Pkm2	X97047	NM_011099
1300	103751_at	0.005089	346.57	189.43	AA409316	AA833096	NM_134087
1301	93509_at	0.005095	2440.13	2091.9	Ube2b	U57690	NM_009458
1302	106463_at	0.005095	443.83	232.4	---	AI850334	XM_129010
1303	93615_at	0.005096	224.6	149.67	Pbx3	AF020200	NM_016768
1304	139493_at	0.005104	1115.77	168.2	C030032C09Rik	AI840105	XM_618798
1305	166816_at	0.005104	3492.67	2573.4	Cul5	AI852817	NM_027807
1306	163689_at	0.005118	1826.83	1399.17	Mte1	AA286242	NM_134188
1307	98475_at	0.005122	288.37	166.33	---	U69262	NM_016762
1308	110581_at	0.005132	1881.9	1019.03	5730405I09Rik	AA189229	NM_026484
1309	AFFX-BioB-M_at	0.005133	3728.1	1675.43	---	J04423	---
1310	113094_at	0.005141	1360.93	523.67	2700038M07Rik	AA175692	NM_019653
1311	98081_at	0.005156	346.93	226.27	Gtf3a	AI853173	NM_009087 /// NM_181730
1312	165698_i_at	0.005165	1254.63	663.57	Zfp261	AI117254	NM_019831
1313	112378_at	0.005173	676.73	488.87	Sh3kbp1	AI842868	NM_021389
1314	165581_at	0.005174	8621.83	6836.47	0710005M24Rik	AI841362	NM_178631
1315	131772_at	0.005176	698.97	369.9	---	AI427604	---
1316	96011_at	0.005204	1494.77	699.97	Matr3	AB009275	NM_010771
1317	104654_at	0.005212	1097.53	731.63	Actl6	AI847687	NM_031404
1318	117005_at	0.005222	4286.03	2829.87	C030033M19Rik	AW124012	NM_001012623 /// NM_001012624 /// NM_001012625 /// NM_053270 /// NM_183018
1319	117178_at	0.005232	1974.23	1314.27	---	AI844448	XM_484616
1320	109105_i_at	0.005236	369.97	126.73	Parva	AW122202	NM_020606
1321	92870_at	0.005242	711.37	356.1	Sel1h	AF063095	NM_011344
1322	108373_at	0.005248	318.57	224.83	B930006L02Rik	AW124108	NM_178764
1323	166513_at	0.005248	1402.9	677.1	C130038G02Rik	AI844429	NM_001033601 /// NM_029920
1324	112072_at	0.005261	1185.47	610.67	---	AW124532	XM_488897
1325	162855_at	0.005268	1356.23	490.77	Btbd14b	AI851205	NM_025788
1326	94970_at	0.005271	351.6	226.27	C230060M08Rik	AI852314	NM_182939
1327	108308_at	0.005275	800.9	544.7	A730011F23Rik	AW124712	XM_620260
1328	111083_at	0.005296	961.37	270.7	Tcf4	AW122341	NM_013685
1329	163885_at	0.005298	1346	820.53	Ube2d3	AA104137	NM_025356
1330	106893_at	0.005314	2810.33	2067.67	Lgi3	AW046096	NM_145219
1331	161616_f_at	0.00535	659.37	413.53	---	AV354117	NM_023396
1332	102030_at	0.005367	170.4	80.43	Atrx	AF026032	---
1333	97451_at	0.00538	911.3	767.37	Mcfd2	AI837599	NM_139295 /// NM_176808
1334	103520_at	0.00541	226.37	74.07	Vegfa	M95200	NM_001025250 /// NM_001025257 /// NM_009505

Table 5

1335	93652_i_at	0.005432	869.97	373.93	Vamp1	U61751	NM_009496	
1336	101367_at	0.005437	4226.53	2633.33	Dctn1	U60312	NM_007835	
1337	165770_at	0.005453	5468.3	4427.33	4833444A01Rik	AI851927	---	
1338	130469_s_at	0.005454	476.07	307.07	Rbm5	AW049099	NM_148930	
1339	165532_r_at	0.005456	5142.43	1436.67	Pum1	AW214087	NM_030722	
1340	105301_at	0.00547	1823.27	1184.33	1700020I14Rik	AW121997	XM_488956	
1341	106936_at	0.005486	859.37	453.4	A230020K05Rik	AI846328	NM_029930	
1342	140699_at	0.005489	776.03	362.7	Gsk3b	AW124014	NM_019827	
1343	92492_at	0.005497	233.43	116.8	Ak3l	AB020203	NM_021299	
1344	112867_at	0.005499	1177.37	540	1600019D15Rik	AI846416	NM_028975 /// NM_030108	
1345	163246_at	0.005534	7265.27	4449.77	Usp22	AA939763	NM_001004143	
1346	94955_at	0.005541	411.33	266.57	5530600A18Rik	AW125433	NM_027799	
1347	97160_at	0.005542	1104.73	464.7	Sparc	X04017	NM_009242	
1348	167463_r_at	0.005548	2373.17	1528.3	Ubqln1	AV233802	NM_026842 /// NM_152234	
1349	109410_at	0.005557	1681.63	1086.63	9230102N17Rik	AW121121	NM_001012518 /// NM_172545	
1350	106581_at	0.005558	3146.6	1986.07	0610042I15Rik	AW049498	NM_019661	
1351	162723_at	0.005579	605.5	416.07	Cacnb4	AW046306	NM_146123	
1352	103967_at	0.005589	94.83	25.1	Mid2	AI551105	NM_011845	
1353	114526_at	0.005618	257.23	138.1	St7l	AI265613	NM_153091	
1354	162834_at	0.005623	918.97	352.43	Ddah1	AW050076	NM_026993	
1355	102316_at	0.005635	662.13	488.1	Capn5	Y10656	NM_007602	
1356	135364_at	0.005652	727	440.73	---	AI506466	---	
1357	160203_at	0.005657	976.8	784.73	5330419I01Rik	AA840409	NM_134081	
1358	137165_at	0.005698	539.6	242.9	---	AI327233	XM_138063	
1359	108490_at	0.005699	1604.8	1184	Pten	AI463227	NM_008960	
1360	105072_at	0.005699	152.8	80.47	A630082K20Rik	C86444	XM_145254	
1361	93618_at	0.0057	4272.2	3346.03	Spnb3	AF026489	NM_021287	
1362	93852_at	0.005703	2455.53	1383.27	Mef2a	AW045443	NM_001033713	
1363	110625_at	0.005716	142.53	50.77	5730538E15Rik	AI591648	NM_173443	
1364	113012_at	0.005724	2570.07	1620.67	Gpd2	AI846919	NM_010274	
1365	113288_at	0.005734	461.17	306.4	Klf3	AA967846	NM_008453	
1366	136244_at	0.005746	1726.53	1223.8	---	AI845568	NM_138682	
1367	138507_at	0.005753	10250.77	7440.2	---	AI852513	---	
1368	98083_at	0.005765	814.7	537.37	Copeb	AW049031	NM_011803	
1369	92183_at	0.005765	1082.07	748.07	Dtna	Z79787	NM_010087 /// NM_207650	
1370	98731_at	0.005769	345.03	184.67	Rab5b	X84239	NM_011229 /// NM_177411	
1371	166605_at	0.005775	1814.87	1192.47	---	AI315686	---	
1372	112648_f_at	0.005809	314.23	131.93	Mtf2	AA623502	NM_013827	

Table 5

1373	112203_at	0.005844	755.6	412.1	Gmfb	AI159117	NM_022023
1374	104354_at	0.005853	1396.97	1039.63	Csf1r	X06368	NM_007779
1375	96178_at	0.005862	1505.53	1006.93	Myst2	AI850636	NM_177619
1376	139224_at	0.005874	2749.97	1474.03	Habp4	AW049540	NM_019986
1377	92445_at	0.005889	317.07	161.03	Cacna1a	U76716	NM_007578
1378	103436_at	0.005898	828.53	491.23	Gtpbp1	U87965	NM_013818
1379	165951_i_at	0.005901	656.4	321.63	BC034507	AI427140	XM_131888
1380	101857_at	0.005903	768.4	376.57	Srpk2	AB006036	NM_009274
1381	160880_at	0.005909	2459.9	1621.83	Mapk8ip3	AB005662	NM_013931
1382	137513_at	0.005913	1559.1	1084.4	Elavl4	AI666779	---
1383	135272_at	0.005916	2621.73	1599.8	C030032C09Rik	AI852221	XM_618798
1384	166810_at	0.005935	23233.1	15988.13	Trim37	AW123384	NM_197987
1385	103611_at	0.005938	4211.93	3078.03	Cd47	AB012693	NM_010581
1386	139147_at	0.005959	713.43	509.4	---	AW121331	---
1387	107426_at	0.005967	449.47	244.57	4932408F19	AW047162	NM_207225
1388	95405_at	0.005971	969.3	709.1	Mesdc2	AW045534	NM_023403
1389	163574_at	0.005977	4355.03	2839.63	Slc4a10	AI849868	NM_033552
1390	106648_at	0.005982	3713.67	2056.93	Cklfsf3	AW045837	NM_024217
1391	160320_at	0.006013	795.67	566.33	Sorbs1	U58883	NM_001034962 /// NM_001034963 /// NM_001034964 /// NM_009166 /// NM_178362
1392	166439_at	0.006015	1955.23	1178.67	Pigb	AI875170	NM_028181
1393	166843_at	0.006018	15151.47	11120.73	---	AI851523	---
1394	160777_at	0.006026	2765.73	2052.27	AA408451	AI851515	XM_127105
1395	98635_at	0.00603	1074.7	653.9	D11Moh35	AI854629	NM_172300
1396	109647_at	0.006032	1519.87	982.07	E030026I10Rik	AI021441	NM_008687
1397	104293_at	0.006034	1368.17	1063.37	1810045K06Rik	AI882440	XM_144142
1398	101564_at	0.006036	358.03	180.3	Cnot7	U21855	NM_011135
1399	106805_at	0.006039	318.03	158.33	9130023D20Rik	AW048267	NM_178746
1400	99196_at	0.00604	3473.47	1792.03	---	AI848532	NM_001024622
1401	109760_at	0.006051	5266	4132.83	Dnajc5	AI848972	NM_016775
1402	166807_at	0.006072	3665.53	2646.03	Kcnj11	AI842722	NM_010602
1403	109679_at	0.006077	2736.23	2003.93	Galntl1	AI841003	XM_283069
1404	107411_at	0.00608	387.57	134.87	Pik3ca	AW048031	NM_008839
1405	109550_at	0.006082	227.03	148.87	1110032A04Rik	AW122199	NM_133675
1406	113855_at	0.00609	3845.8	2671.67	---	AI840093	NM_001029877
1407	92518_at	0.006091	504.77	411.57	Neo1	Y09535	NM_008684
1408	162978_at	0.006148	684.4	471.17	BB075781	AI840731	NM_027712 /// NM_177639
1409	163300_at	0.006154	411.9	306.47	2610206B13Rik	AI842125	NM_026047

Table 5

1410	111211_at	0.006173	2323.23	1391.4	---	AW122869	NM_198105
1411	110643_at	0.006178	387.63	263.9	Crlz1	AI616280	NM_023054
1412	104327_at	0.006195	1099.97	640.17	9030612M13Rik	AA755234	---
1413	111080_at	0.00621	559.6	336.9	E230022H04Rik	AA762313	NM_153515
1414	162985_at	0.006215	1336.23	565.93	Pbx1	AI848790	---
1415	92374_at	0.006218	789.93	568.4	---	AW120691	NM_001008533 /// NM_009629
1416	99432_at	0.006222	285.97	162.87	Cyln2	AJ228865	NM_009990
1417	93341_r_at	0.006234	3731.17	3026.17	Copb2	AF043120	NM_015827
1418	98596_s_at	0.006235	1477.97	1036.97	Siat9	Y15003	NM_001035228 /// NM_011375
1419	116929_at	0.006243	1056.1	776.73	---	AI835351	---
1420	135785_at	0.006275	325.27	27.3	---	AI836579	XM_356997
1421	99146_at	0.006303	645.83	489.57	Stx6	AW124355	NM_021433
1422	112768_at	0.006305	1399.63	517.3	Utrn	AI227355	NM_011682
1423	109499_at	0.006312	694.77	443.5	4930565N16Rik	AA990018	XM_125517
1424	96375_at	0.006313	144.07	97.03	---	C80249	---
1425	138524_r_at	0.006336	3953.53	2722.57	9530033F24Rik	AI836314	XM_622106 /// XM_622111
1426	98841_at	0.006357	222.33	147.07	Acvr2	M65287	NM_007396
1427	92769_at	0.006359	2172.7	1616.03	Psmd3	M25149	NM_009439
1428	105878_at	0.006361	499.07	230.6	---	AI846717	---
1429	166321_at	0.006381	972.8	473.17	Cdc37l	AI851215	NM_025950
1430	95142_s_at	0.006401	3681.53	2150.77	Capzb	U10407	NM_009798
1431	160936_at	0.00643	308.4	225.33	Tram1	AA763937	NM_028173
1432	111382_at	0.006434	36045.3	27935.8	Calm1	AI835341	NM_009790
1433	109329_at	0.006438	373.27	143.97	6430526O11Rik	AA915457	XM_110937
1434	166213_at	0.006442	1319.47	969.8	2410089E03Rik	AW121869	XM_127911
1435	95335_at	0.006443	692.07	462.17	Cx3cr1	AF074912	NM_009987
1436	99445_at	0.006455	169.5	122.13	1110028E10Rik	AW047012	NM_152808
1437	166740_at	0.006461	2266.7	1762.27	D16Wsu109e	AA624602	---
1438	109651_at	0.006469	196.73	125.5	Socs2	AA764618	NM_007706
1439	168018_at	0.006472	876.03	571.73	BC003322	AI154887	NM_030257
1440	AFFX-CreX-5_st	0.006473	202.03	110.93	---	X03453	---
1441	111335_at	0.006498	1794.23	1082.87	1110019L22Rik	AW122435	NM_026756
1442	114055_at	0.00651	1861.93	1350.2	---	AI848667	---
1443	98872_at	0.006516	351.4	163.37	Ugt8	U48896	NM_011674
1444	93752_at	0.006519	888.57	743.3	E430001P04Rik	AI848393	NM_172015
1445	101483_at	0.006548	1842.5	1506.4	Ccndbp1	AI850862	NM_010761
1446	100494_at	0.00655	320.37	207.63	Fgf1	M30641	NM_010197
1447	162057_f_at	0.006565	544.4	305.73	---	AV269118	NM_026002

Table 5

1448	163820_at	0.006576	435.87	297.4	Csnk2a2	AW122718	NM_009974
1449	139123_at	0.006584	4033.37	1904.63	Syngr1	AI854087	NM_009303 /// NM_207708
1450	112330_at	0.006586	2086.6	1524.93	Fbxo25	AI847020	NM_025785
1451	137584_f_at	0.006588	1689.27	1059.4	---	AI504044	---
1452	139403_s_at	0.006588	2537.57	1216.93	Dgcr2	AI643076	NM_010048
1453	92673_at	0.006604	811.77	470.33	Sh3gl2	U58886	NM_019535
1454	134281_at	0.006613	1760.8	1251.8	Pde7b	AI551165	NM_013875
1455	112804_at	0.006632	4820.3	3124.9	1500001H12Rik	AI849194	NM_021316
1456	139196_at	0.006646	155.57	58.67	1190030G24	AW047739	XM_622107
1457	104361_at	0.006661	598.73	500.37	LOC232337	AI837260	NM_177684
1458	166874_r_at	0.006675	4354.37	2501.43	LOC381325	AI852300	---
1459	94105_at	0.006695	1465.13	1010.5	Cdc42	L78075	NM_009861
1460	107354_at	0.006704	3892.87	2621.4	Slitrk5	AW049472	NM_029273 /// NM_198865
1461	112963_at	0.006732	363	177.43	Zfp120	AI315103	NM_023266 /// NM_181266 /// NM_181267
1462	110169_at	0.006738	557.2	218.5	Pdxk	AW214049	NM_172134
1463	112874_at	0.00674	3524.6	2195.43	Ppp3ca	AW123588	NM_008913
1464	138007_at	0.006741	3497.7	1878.37	---	AI851235	NM_011323
1465	105700_at	0.006761	8505.3	4190.5	Syt1	AW125093	NM_009306
1466	106483_at	0.006772	321.2	227.1	2410014A08Rik	AI850530	NM_175403
1467	93309_at	0.006798	702.9	320.13	Ddx3x	U42386	NM_010028
1468	115376_at	0.006801	1297.93	765.53	4933439F18Rik	AI850511	NM_025757
1469	98960_s_at	0.006828	580.67	339.5	B3galt3	AF029792	NM_020026
1470	163285_at	0.006835	451.07	359.43	Rai14	AI853224	NM_030690
1471	100713_at	0.006859	211.83	124.1	LOC170938	AB020542	NM_133358
1472	110569_at	0.006875	251.9	137.13	AW556347	AW121158	NM_183186
1473	111761_at	0.006911	6308.27	4450.93	Pde1a	AW125737	NM_001009978 /// NM_001009979 /// NM_016744
1474	AFFX-BioC-3_at	0.006943	4018.07	1730	---	J04423	---
1475	96655_g_at	0.006944	790.8	516.4	8430408H12Rik	AI852916	NM_026236
1476	113597_g_at	0.006949	2283.83	1461	4931406I20Rik	AI842100	NM_025739
1477	115058_at	0.006951	1120.33	762.37	---	AA756546	---
1478	164120_at	0.006959	509.33	279.47	Rpe	AI326009	NM_025683
1479	96592_at	0.006965	835.27	403.37	Pik3r1	U50413	NM_001024955 /// NM_011085
1480	115021_at	0.006976	1446.33	607.5	2810468K05Rik	AI390477	XM_484053
1481	160483_at	0.007019	2342	1530.63	Tcf4	U16322	NM_013685
1482	164219_at	0.007021	1032.83	715.6	Phc3	AA967551	NM_153421
1483	92461_at	0.007024	944.37	709.53	Mmp17	AB021224	NM_011846
1484	110518_at	0.007082	1075.63	592.13	0710005I19Rik	AW123483	NM_001007569

Table 5

1485	114130_at	0.007083	679.9	468.17	Ap3s2	AI843423	NM_009682
1486	133833_at	0.007091	1712.5	1397.03	---	AA210380	---
1487	117035_at	0.007113	1292.43	815.1	Atp8a1	AI853962	NM_009727
1488	103842_at	0.007116	524.63	205.27	Ddx3y	AJ007376	NM_012008
1489	95472_f_at	0.007126	1334.93	899.47	Uqcrb	AI526902	NM_026219
1490	113534_at	0.00715	349.17	212.07	Trpc4ap	AA821949	NM_019828
1491	100592_at	0.00717	2068.57	1465.3	Ghitm	AI929971	NM_078478
1492	93635_at	0.007177	1216.33	961.07	Kif3c	AF013116	NM_008445
1493	135312_at	0.007186	3882.57	2941.37	Bral2	AI841064	NM_177900
1494	111990_at	0.007211	737.33	601.4	Lman2l	AI843115	NM_001013374
1495	104591_g_at	0.00722	2197.43	1446.23	Mef2c	L13171	NM_025282
1496	93614_at	0.007224	474.83	312.13	Rragd	AA600647	NM_027491
1497	111138_at	0.007226	573.8	369.23	---	W91678	XM_126551
1498	166664_at	0.007226	514.73	251.43	1200009K13Rik	AV298782	NM_025814
1499	93667_at	0.007238	2698.57	1937.37	Fbxw7	AW120511	NM_080428
1500	112459_at	0.00724	1023.9	811.53	Mapkap1	AW123352	NM_177345
1501	112862_at	0.007246	1651.57	704.43	Agpat3	AI839358	NM_053014
1502	96884_at	0.007249	576.53	444.63	Carhsp1	AI847631	NM_025821
1503	116694_at	0.007255	1688.7	1070.03	BC018242	AI413751	NM_144935
1504	160760_at	0.007256	767.7	555.1	Ptprk	L10106	NM_008983
1505	106978_at	0.007257	599.63	434.13	4733401N12Rik	AI843004	NM_001013391
1506	108575_at	0.007268	3140.3	2584.33	Egfl5	AI842010	---
1507	114064_at	0.007281	619	414.57	Eya3	AI844637	NM_010166 /// NM_210071 /// NM_211356 /// NM_211357
1508	93803_at	0.007285	1211.07	943.83	Psme3	AB007139	NM_011192
1509	137501_f_at	0.007292	749.9	407.13	2010007L18Rik	AI529536	NM_007386
1510	98538_at	0.007305	845.33	615.83	2610507B11Rik	X81632	NM_001002004
1511	110163_at	0.007308	870.1	566.2	---	AW259659	NM_180600
1512	130911_at	0.007313	3565.47	2255.23	---	AI197367	---
1513	161467_f_at	0.00734	2021.1	1730.43	---	AV348528	NM_009721
1514	162676_at	0.007346	1449.7	913.3	Glcci1	AA647842	NM_133236 /// NM_178072
1515	108748_g_at	0.007348	564.67	330.73	---	AI553620	---
1516	93583_s_at	0.007349	578.9	432.87	Igh-6	V00817	XM_177464 /// XM_484186
1517	109790_at	0.007358	356.67	194.1	---	AI414473	NM_019431
1518	98580_at	0.007361	1480.17	979.3	Ppm1a	D28117	NM_008910
1519	162631_at	0.00737	389.07	279.17	G430022H21Rik	AI594352	NM_201638
1520	110606_at	0.007372	903.73	624.63	D2Bwg1356e	AW122417	XM_130523
1521	107582_at	0.007396	1446.73	934.73	---	AW050026	---
1522	102835_at	0.007431	782.07	582.47	Ap2a2	X14972	NM_007459

Table 5

1523	106990_at	0.007471	1646.43	674.97	A830007M12	AI843411	NM_198250
1524	106925_at	0.00751	559.63	408.67	9630033F20Rik	AW125887	NM_177003
1525	111131_g_at	0.007513	690.03	410.63	4933435E07Rik	AW123159	NM_173180
1526	112756_at	0.007516	1022.4	769.6	1810009A16Rik	AA050204	XM_355528
1527	107009_at	0.007528	7079.4	4280.33	---	AI842805	---
1528	110986_at	0.007556	587.23	350.27	B230205M03	AI046348	---
1529	134152_at	0.007557	326.37	185.17	6030490I01Rik	AA208287	NM_177359
1530	104414_at	0.007558	846.07	567.93	Gnao	AW050194	NM_010308
1531	114622_at	0.007558	1175.73	605.07	3830421F13Rik	AI850440	NM_027226
1532	99501_at	0.007582	707.17	281.9	3100002M17Rik	AA882416	NM_027016
1533	99459_f_at	0.007605	335.93	97.4	Mark2	X70764	NM_007928
1534	96596_at	0.007623	1231.3	926.2	Ndr1	U52073	NM_008681 /// NM_010884
1535	111123_s_at	0.007641	2866.83	1954.5	Metap1	W63868	NM_175224
1536	134688_at	0.007643	274.9	68.97	Foxp2	AI449000	NM_053242 /// NM_212435
1537	136174_at	0.007654	2965.07	2384.3	---	AW048956	---
1538	163719_at	0.007658	412.4	270.23	0610011N22Rik	AI591477	NM_024201
1539	134039_at	0.007683	3816.77	1298.23	Gng2	AA253748	NM_010315
1540	129315_at	0.007695	1153.03	386.07	BC035291	AI122193	---
1541	94737_at	0.007703	481.03	283.63	Adcy8	U85021	NM_009623
1542	114536_at	0.007704	577.2	369.33	1810013L24Rik	AA792997	XM_148044 /// XM_622721
1543	109709_at	0.007718	1071.13	691.83	2810489O06Rik	AW124034	NM_175386
1544	115217_at	0.007726	744.07	591.27	Nfat5	AI852272	NM_018823 /// NM_133957
1545	97097_at	0.007732	397.87	258.13	4732465J09Rik	AW125669	XM_356161
1546	109570_at	0.007743	488.1	285.67	1110015E18Rik	AA763178	NM_026536
1547	93446_at	0.007747	83.2	28.53	---	U48721	NM_009560
1548	107466_at	0.007779	500	272.63	---	AW045897	NM_001014390
1549	96464_at	0.007785	409.97	299.6	Plxnb2	N28179	XM_484491
1550	93235_at	0.007793	230.8	130.7	BB128963	AI020029	NM_172742
1551	108471_at	0.007799	267.33	177.27	9030416H16Rik	AW105925	---
1552	113182_at	0.007805	319.5	154.43	Hdlbp	AI844871	NM_133808
1553	160517_at	0.007811	218.83	169.93	Lmnb1	M35153	NM_010721
1554	99154_s_at	0.007823	449.3	404.93	1810020D17Rik	AW122625	NM_183251
1555	114982_at	0.007837	1835.07	1416.93	Prkaa2	AA959852	NM_178143
1556	112157_at	0.00784	1189.03	597.07	9430077C05Rik	AW122374	XM_619731 /// XM_622875
1557	96255_at	0.007844	1566.93	1260.23	Bnip3l	AF067395	NM_009761
1558	104176_at	0.007863	127.03	76.1	C79663	AI850941	NM_177762
1559	166096_f_at	0.007895	1385.67	775.97	2900054P12Rik	AW125683	NM_028407
1560	136056_at	0.007909	2762.03	1374.4	Mapk8	AA645429	NM_016700

Table 5

1561	162906_at	0.007913	344.83	251.03	1110001M19Rik	AA793025	NM_001024205
1562	162722_at	0.00792	2065.5	1363.93	BC043098	AI845023	NM_174997
1563	96913_at	0.007941	1226.8	875.4	---	AW122615	NM_145558
1564	104432_at	0.007966	1462.47	1155.63	Arhn	AF016482	NM_009708
1565	92519_at	0.007989	243.37	151.17	Phka1	X74616	NM_008832 /// NM_173021
1566	104407_at	0.007996	880.43	588.73	Alcam	L25274	NM_009655
1567	94478_at	0.007999	2578.87	2176.3	---	AI841377	NM_025887
1568	163781_at	0.008001	198.17	156.5	2810407C02Rik	AI842531	XM_283848
1569	116987_at	0.00804	969.23	610	4631434O19Rik	AI842482	XM_130859
1570	167447_f_at	0.008046	741.67	539.37	AW260253	AV276666	NM_172930
1571	160287_at	0.008068	2016.8	1310.97	Map1lc3	AI852557	NM_026160
1572	110674_at	0.008072	1614.03	888.97	Sbno1	AA105753	XM_355637
1573	166011_i_at	0.008072	644.13	337.4	Rab3c	AV159057	NM_023852
1574	105651_g_at	0.008077	2314.93	1560.37	---	AI315312	NM_178764
1575	95522_i_at	0.008078	446.27	294.7	Zfp68	AB024005	NM_013844
1576	92378_at	0.008094	635.97	373.2	Ptprz1	AI849305	XM_620293
1577	136733_at	0.008095	1768.2	1227.1	---	AI850939	---
1578	94511_at	0.008097	280.63	161.13	---	AI850546	NM_025965
1579	96674_at	0.008098	1008.17	814.2	Tnpo3	AW123553	NM_177296
1580	168021_at	0.008099	622.5	193.57	2900052N01Rik	AV153111	---
1581	107619_s_at	0.008118	1786.97	631.63	---	AW120573	XM_132143
1582	135351_i_at	0.008159	1238.97	884.3	MGC38922	AA914469	NM_144842
1583	101914_at	0.008166	1118.63	751.57	D1Ertd396e	AI846484	NM_021421
1584	133553_at	0.00817	265.6	65.57	---	AI595843	NM_025683
1585	93358_at	0.008176	684.57	487.67	1500010B24Rik	AI836451	NM_025437
1586	111384_at	0.008178	323.63	207.57	Zfp191	AI019086	NM_021559
1587	96878_at	0.008189	298.9	142.8	1810044O22Rik	AW048566	NM_025558
1588	111262_at	0.00819	641.9	449.6	Dusp11	AW061180	NM_028099
1589	171557_i_at	0.008191	562.53	281.53	---	AV116073	NM_172148
1590	160270_at	0.008203	815.63	527.63	Lman1	AW108371	NM_027400
1591	166812_at	0.008205	2438.3	1500.53	Kcnq5	AI844221	NM_023872
1592	107029_at	0.008237	691.53	589.73	E130306I01Rik	AW048342	NM_145471
1593	163642_at	0.008271	585.17	347.73	---	AI840898	NM_010315
1594	160843_at	0.008272	495.47	215.43	Spin	AA796214	NM_011462 /// NM_146043
1595	113629_at	0.008284	361.07	180.37	Stam2	AW047341	NM_019667
1596	110858_at	0.008299	4961.6	3251.53	B930006L02Rik	AW121823	NM_178764
1597	107910_at	0.008301	351.07	217.5	Cdadc1	AW124595	XM_127813
1598	117316_at	0.008347	618.9	448.37	Gpd2	AW124811	NM_010274

Table 5

1599	170044_s_at	0.008356	2245.9	1454.23	---	AV302009	NM_019774
1600	140640_at	0.008383	764.63	327.87	Cbx5	AI451142	NM_007626
1601	101138_at	0.008394	407.23	159.13	Gabrb2	U14419	NM_008070
1602	166666_at	0.008409	2220.63	1458.77	4732496O08Rik	AV369609	NM_172877
1603	97724_at	0.008415	811.73	461.6	Cry2	AB003433	NM_009963
1604	97530_at	0.008421	1418.4	994.57	Ube2i	U82627	NM_011665
1605	92186_at	0.008435	166.13	87.7	Arx	AB006103	NM_007492
1606	92899_at	0.008451	339.87	122.4	Gad2	D42051	NM_008078
1607	110028_at	0.008453	133.43	59.43	---	AW124261	XM_129972
1608	98778_at	0.00849	1455.27	1076.43	D5Ertd606e	AI837543	NM_001009818
1609	113119_at	0.008511	637.53	422.17	Ddx42	AI835854	NM_028074
1610	107412_at	0.008511	471.93	291.4	---	AW048881	NM_201406
1611	129853_at	0.00852	12607.47	7835.73	C530050K14	AI838690	NM_001024955 /// NM_011085
1612	100980_at	0.008533	213.2	127.43	Rock1	U58512	NM_009071
1613	92220_s_at	0.008542	2501.77	1745.47	Bin1	U60884	NM_009668
1614	161086_at	0.008551	117.8	41.73	Lin7c	AF087695	NM_011699
1615	114066_at	0.008553	724.77	380	Cugbp1	AI844119	NM_017368 /// NM_198683
1616	133711_at	0.008557	2601.83	1227.9	---	AI462512	NM_153057
1617	103090_at	0.008578	592.03	403.2	2410003P15Rik	AI838742	NM_018888
1618	129134_s_at	0.008589	1611.17	1211	Ebna1bp2	AA656774	NM_026932
1619	135441_at	0.008622	727.03	410.37	D8Ertd457e	AA673815	NM_181854
1620	110423_at	0.008629	2057.87	1192.77	2810425F24Rik	AA895554	NM_001003946
1621	108915_at	0.008669	241.03	108	Slc17a6	AI841371	NM_080853
1622	130343_at	0.008677	5623.9	4699.57	---	AU016810	NM_001025192 /// NM_009988
1623	99991_at	0.008693	440.67	298.47	Il17r	U31993	NM_008359
1624	138513_at	0.008704	1357.9	611.93	---	AI853785	---
1625	112325_at	0.008725	2969.47	2741.43	Bap1	AW124035	NM_027088
1626	104645_at	0.008739	628.57	420.27	Klf7	AI853712	NM_033563
1627	110752_at	0.008748	2609.4	1310.47	9430022M17Rik	AW122288	NM_010905
1628	139531_at	0.008748	835	388.83	Syt6	AW120795	NM_018800
1629	115489_at	0.00876	7796.57	5344.07	Dpysl2	AI851130	NM_009955
1630	166681_at	0.008777	9765.77	6038.37	D130060C09Rik	AI447884	NM_177054 /// NM_199038
1631	92952_f_at	0.008782	3208.53	1484.47	Napb	X61455	NM_019632
1632	115922_i_at	0.008791	422.33	280.23	Cdh13	AI550332	---
1633	104461_at	0.0088	693.57	264.67	Pik3ca	AW121773	NM_008839
1634	106975_at	0.008801	22452.6	13971.27	Atp1a3	AI837081	NM_144921
1635	110682_at	0.008806	1573.6	1103.8	---	AW060479	XM_149712
1636	101998_at	0.008813	118.4	84.27	4833420G17Rik	AW125086	NM_026127

Table 5

1637	114121_at	0.008824	1750.17	1096.63	Sec1512	AI462110	XM_355790
1638	98364_at	0.008846	276.2	142.8	Kcnd2	AF107780	NM_019697
1639	104214_at	0.008871	267.33	203.77	Slc7a8	AW122706	NM_016972
1640	110857_at	0.008876	1172.2	902.37	Rab6ip2	AW123950	NM_053204 /// NM_178085
1641	94244_at	0.00892	1106.57	766	Ihpk1	AW123807	NM_013785
1642	110824_at	0.008934	3027.83	1723	Slc1a3	AW121315	NM_148938
1643	113901_at	0.008999	2758.2	1549.2	Cap2	AI593827	NM_026056
1644	111229_at	0.009007	634.33	329.8	Slc38a2	AW123416	NM_175121
1645	103402_at	0.009031	837.13	583.07	Tm7sf3	AI848522	NM_026281
1646	101590_at	0.009036	429.5	231.3	Lamp2	AI747194	NM_001017959 /// NM_010685
1647	140546_at	0.009043	10593.83	6101.23	Gfap	AI835926	---
1648	167569_at	0.00905	812.4	578.33	AA959934	AI467162	NM_153167
1649	167886_f_at	0.009062	622.57	340.87	Rnf138	AV205813	NM_019706 /// NM_207623
1650	102059_at	0.009106	1187.93	873.27	Nicn1	AW125418	NM_025449
1651	115067_at	0.009109	355.1	209.53	Sec8	AW048324	NM_009148
1652	104524_at	0.009112	1628.5	1110	1110001F24Rik	AI842825	NM_019821
1653	138947_at	0.009139	4408.4	3263.47	Kcnip2	AI851528	NM_030716 /// NM_145703 /// NM_145704
1654	115879_at	0.009144	3088.17	2235.73	1700012G19Rik	AI837146	NM_025954
1655	115831_at	0.009149	934.3	764.2	---	AI837224	NM_139141
1656	134822_at	0.009152	1016.27	693.97	---	AI605231	---
1657	106442_at	0.009156	1866.3	1060.97	Gng7	AI850107	NM_010319
1658	136245_at	0.009156	980.47	476.07	Zdhhc2	AI845904	NM_178395
1659	107393_at	0.009163	465.27	272.27	Rbm5	AI502997	NM_148930
1660	114030_at	0.009165	450.5	299.43	DXImx41e	AI851819	NM_173747
1661	111877_at	0.009192	1419.23	1141.93	---	AA939957	---
1662	97090_at	0.009215	151.63	99.63	Tcf20	U20282	NM_013836
1663	108745_at	0.009217	479.03	263.27	9630050M13Rik	AI466491	XM_194000
1664	98827_i_at	0.009222	333.53	109.3	Kif5a	X61435	NM_008449
1665	163313_at	0.009242	526.3	199.83	---	AI648173	XM_486329
1666	101529_g_at	0.009258	926.67	569.53	Tceal	D00925	NM_011541
1667	112204_at	0.009258	237.67	133.77	Gclm	AA636892	NM_008129
1668	93659_at	0.009316	783.47	206.73	Camk2a	X14836	NM_009792 /// NM_177407
1669	101919_at	0.009362	279.73	222.2	Zfx	M32309	NM_011768
1670	113596_at	0.009364	2148.83	1456.57	4931406I20Rik	AI842100	NM_025739
1671	93144_at	0.00937	1813.87	1496.87	AI317237	AI854602	NM_172819
1672	162919_at	0.009378	614	238.4	D930036B08Rik	AI227478	NM_198649
1673	100472_at	0.00942	930.63	448.7	Enah	D10727	NM_010135
1674	100037_at	0.009435	211.53	109.37	---	AW213225	NM_025860

Table 5

1675	104109_at	0.009479	998.03	700.13	4930438M06Rik	AI853773	NM_145564
1676	138054_at	0.009489	5233.07	3361.27	Faim2	AI835515	NM_028224
1677	93716_at	0.009497	789.1	551.03	Trim46	U16175	NM_017403 /// NM_183037
1678	112481_at	0.009508	2948.4	1916.67	BC008150	AI852227	XM_484507
1679	115553_at	0.009509	9978.67	6896.73	Purb	AI841779	NM_011221
1680	93298_at	0.009512	1643.57	1136.63	Papss1	U34883	NM_011863
1681	112861_at	0.009513	1582	1010.23	Rassf3	AI839168	NM_138956
1682	160457_at	0.009525	6585.3	4888.47	9130413I22Rik	AW125397	NM_026242
1683	100708_at	0.009526	4070.13	3378.93	H3f3b	X13605	NM_008211
1684	98528_at	0.009527	1498.27	1303.03	2510006D16Rik	AI854901	NM_029748
1685	115382_at	0.009528	809.03	559.83	Etohi2	AI874853	NM_026799
1686	111659_at	0.00953	552:93	441.07	---	AI120758	---
1687	101973_at	0.009535	1046.63	807.97	Cited2	Y15163	NM_010828
1688	116518_at	0.009549	762.53	394.57	---	AI509356	---
1689	100139_at	0.009555	7196.13	5687.6	Pcsk1n	AI841733	NM_013892
1690	104058_at	0.009556	2708.33	2219.4	1110018J12Rik	AW047528	NM_028658
1691	111806_at	0.009572	2259.57	1473.23	Pum1	AI848885	NM_030722
1692	93054_at	0.009595	4271.87	3052.73	1110054N06Rik	AI846368	NM_175134
1693	160387_at	0.009595	197.8	159.77	1110055L24Rik	AI853900	NM_025422
1694	112505_at	0.009598	1381.4	971.27	1110030H18Rik	AI851182	NM_026805
1695	167611_at	0.009611	1370.4	822.13	Abcf2	AV214932	NM_013853
1696	96716_at	0.009619	1476.97	1287.03	1110003E01Rik	AW121102	NM_133697
1697	94055_at	0.009621	316.27	153.97	Cttn	U03184	NM_007803
1698	98922_at	0.009634	315.8	253.47	Itm1	L34260	NM_008408
1699	107091_at	0.009634	1355.9	847.27	4121402D02Rik	AI853096	NM_028722
1700	162677_at	0.009654	1179.13	969.5	Fath	AA647211	---
1701	99663_g_at	0.009667	709.6	583.53	Pcnt2	AI194767	NM_001002929
1702	98513_at	0.009667	1228.23	922	0610033N12Rik	AI851821	NM_019988
1703	101980_at	0.009704	643.57	409.97	Rpo2tc1	J03750	NM_011294
1704	104041_at	0.009706	3885.93	2505.73	1810009A16Rik	AW122255	XM_355528
1705	160308_at	0.009728	303.7	200.8	Msn	AI839417	NM_010833
1706	95800_s_at	0.009737	128.93	50.9	---	X53250	NM_009540 /// NM_011768
1707	96002_at	0.009744	735.57	603.83	4921505F14Rik	AW123936	NM_025783
1708	99010_at	0.009753	541.47	453.8	Islr	AB024538	NM_012043
1709	106606_at	0.009755	1950.27	1601.4	Mfn2	AI854053	NM_133201
1710	114397_at	0.009779	1874.17	1540.63	9030409G11Rik	AI843245	NM_144531
1711	93261_at	0.009794	934.03	716.27	Lgmn	AJ000990	NM_011175
1712	93660_at	0.009807	1279.73	348.1	Camk2a	X87142	NM_009792 /// NM_177407

Table 5

1713	130476_at	0.009811	3099.63	2014.8	Ablim2	AW121090	NM_177678
1714	105699_at	0.009823	680.83	385.7	6330509G02Rik	AI845957	NM_172946
1715	100888_at	0.009825	321.83	139.3	Sorl1	AB015790	NM_011436
1716	110678_at	0.009831	779.77	544.13	1110003A17Rik	AA259774	NM_026741
1717	115550_at	0.009837	2411.37	1437.83	Prkca	AI838164	---
1718	163745_at	0.009861	892.8	436.73	A430107J06Rik	AA914620	NM_207633
1719	138980_f_at	0.00987	3303.37	2186.5	B230217C12Rik	AI840637	XM_484073
1720	107448_at	0.009871	984.4	679.23	---	AW048685	---
1721	99191_at	0.009888	6885.9	5242.97	Cri1	AI844939	NM_025613
1722	167776_i_at	0.0099	423.5	259.23	C430017H16	AI121941	XM_143616
1723	116971_at	0.009941	867.3	615.3	AW050020	AI846954	NM_172943
1724	94542_at	0.009942	265.17	168.2	Mbtd1	AA929348	NM_134012
1725	94088_at	0.009954	700.77	387.13	Ptbp2	AW228429	NM_019550
1726	95288_i_at	0.009967	697.97	294.67	A430106J12Rik	AA189811	NM_176841
1727	AFFX-BioC-5_at	0.00997	1689.47	948.63	---	J04423	---
1728	110159_at	0.00997	1324.9	1021.03	4930538C18Rik	AW123686	NM_029457
1729	115035_at	0.009975	251.27	150.63	1700009P03Rik	AI447318	NM_134077
1730	100538_at	0.009981	2619.27	1878.97	Sod1	M35725	NM_011434

Table 6

%Monocular deprivation (16 days) versus control
%Downregulated in long term MD
%Significance criterion = 0.01
%

%i	affyid	p	MD	control	gene		
1	92610_at	0.000733	259.1	470.47	Rdbp	M21332	NM_138580
2	92625_at	0.008408	1193.87	1530.67	Nme2	X68193	NM_008705
3	92628_at	0.005435	1887.17	2942	Rpl36	X75895	NM_018730
4	92631_f_at	0.009236	1983.52	3304.1	Calm3	M19380	NM_007590
5	92636_f_at	0.003608	913.88	1331.43	Sec61g	U11027	NM_011343
6	92768_s_at	0.002068	429.53	909.2	Alas2	M15268	NM_009653
7	92798_at	0.002359	3051.12	3880.47	Atp5c1	AA870675	NM_020615
8	93008_at	0.000837	569.48	875.83	Lsm4	AW120557	NM_015816
9	93019_at	0.007564	859.07	1196.83	H2afx	Z35401	NM_010436
10	93048_at	0.000008	571.35	925.33	Clpp	AJ005253	NM_017393
11	93094_at	0.003971	114.22	203.83	Cdr2	U88588	NM_007672
12	93119_at	0.000094	3974.18	6057.97	Cox5b	X53157	NM_009942
13	93257_at	0.003195	834.02	1083.17	Ddx1	AW048287	NM_134040
14	93519_s_at	0.009139	1367.95	2200.8	Nedd8	AI847056	NM_008683
15	93559_at	0.007186	685.6	1034.2	Apex1	D90374	NM_009687
16	93589_at	0.001711	1611.7	2411.53	Lysal1	AI851172	NM_026174
17	93764_at	0.002064	1091.97	1626.07	2700054G14Rik	AI854527	NM_023312
18	93789_s_at	0.009533	500.92	703.63	Sin3b	AF038848	NM_009188
19	94062_at	0.000674	2352.55	3822.07	Ndufv2	AI847609	XM_128725
20	94068_at	0.003851	1294.02	1688.73	Rps19	AW048899	NM_023133
21	94229_at	0.006025	1560.1	2086.77	0610009M14Rik	AW124489	NM_023910
22	94242_at	0.002521	338.42	522.33	D11Ertd672e	AA881309	NM_026559
23	94806_at	0.005224	1179.5	1586.9	---	AW125336	NM_024221
24	94807_at	0.006567	899.03	1205	Slc25a1	AI848354	NM_153150
25	94850_at	0.005383	299.17	455.5	Acate3	AJ238894	NM_019736
26	94875_at	0.000744	385.67	646.6	Mrpl20	AI838915	NM_025570
27	94897_at	0.005812	811.83	1189.87	Gpx4	D87896	NM_008162
28	95477_at	0.007402	929.23	1636.57	1110001M20Rik	AW125185	NM_029565
29	96041_at	0.007153	869.33	1509.03	Rbm3	AB016424	NM_016809
30	96054_f_at	0.006022	248.43	357.67	Acp1	Y17345	NM_021330
31	96060_at	0.005014	290.37	380.83	Serpinb6a	U25844	NM_009254
32	96617_at	0.009867	754.6	1148.3	Drap1	AI844737	NM_024176

Table 6

33	96709_at	0.003341	4179.12	7394.83	1110008P14Rik	AI839839	NM_198001
34	97204_s_at	0.000624	172.22	362.53	Dnajd1	AI850983	NM_025384
35	97229_at	0.004304	519.65	759.23	5730427N09Rik	AW061042	NM_021552
36	97241_at	0.006237	393.1	648.87	D19Ertd721e	AI787713	NM_146093
37	97274_at	0.004015	946.47	1346.67	Psmd14	Y13071	NM_021526
38	98936_at	0.006461	720.93	1003.93	Sars1	AI837395	NM_011319
39	98937_at	0.004035	834.98	1032.37	Tbrg1	AW049795	NM_025289
40	94526_at	0.003127	1646.85	2518.37	D10Ertd214e	AI848453	NM_134007
41	94530_at	0.008075	433.87	628.8	C85417	AI840376	NM_145445
42	95044_at	0.000001	625.47	1096.03	1500003D12Rik	AI844549	NM_025895
43	95046_s_at	0.00741	762.63	1067.57	Eif2b4	M98036	NM_010122
44	95053_s_at	0.00082	2508.5	3917.9	Sdhb	AA674669	NM_023374
45	95131_f_at	0.000864	5476.75	6840.3	Ndufb2	AI852592	NM_026612
46	95132_r_at	0.008433	4074.27	6418.43	Ndufb2	AI852592	NM_026612
47	95137_at	0.004919	487.02	749.37	1810014L12Rik	AI852985	NM_133706
48	95689_at	0.009342	1464.07	2059.57	Mtch1	AI840995	NM_019880
49	95696_at	0.00036	1590.53	2447.6	Txnl2	AI840882	NM_023140
50	95701_at	0.005204	940.08	1381.9	4930415K17Rik	AW124069	NM_133687
51	95707_at	0.002178	1023.92	1793.7	2900010M23Rik	AA615853	NM_026063
52	96258_at	0.003014	2101.02	4019.6	Mgst3	AI843448	NM_025569
53	96290_f_at	0.003834	5406.58	7332.5	Gtf3a	U93863	NM_019647
54	96318_at	0.009638	685.28	914.27	I125	AW045739	NM_080837
55	96864_at	0.0079	384.93	494.9	AI648866	AI848770	NM_207207
56	96900_at	0.003876	5343.98	8428.83	1620401E04Rik	AW125480	NM_175329
57	96902_at	0.002162	154.33	268.27	2900091E11Rik	AW121847	NM_026070
58	97443_at	0.007506	1497.6	1860.07	Mrpl52	AI850850	NM_026851
59	97518_at	0.009573	1035.65	1698	Fdft1	D29016	NM_010191
60	98125_at	0.004121	649.85	1009.53	1110025I09Rik	AI849193	NM_026795 /// NM_178056
61	98147_at	0.006596	1500.4	2081.33	Usp5	AC002397	NM_013700
62	98588_at	0.007687	523.82	740.7	Fah	Z11774	NM_010176
63	98627_at	0.005161	591.02	1011.2	Igfbp2	X81580	NM_008342
64	99106_at	0.002248	2180.33	3023.73	Cops6	AF071315	NM_012002
65	99123_s_at	0.008858	471.33	703.93	---	AW061280	NM_019502
66	99128_at	0.009963	2669.78	3867.43	---	AI849767	NM_138597
67	99150_at	0.004739	343.48	497.93	Ict1	AI844357	NM_026729
68	99607_at	0.002588	2438.88	3859	Skp1a	Z47088	NM_011543
69	99656_at	0.000127	451.6	740.63	D8Ertd812e	AI849027	NM_198020
70	100040_at	0.009841	205.78	298.7	Mrpl17	AI843081	NM_025301

Table 6

71	100042_at	0.002091	708.95	1056.7	Hagh	AI837921	NM_024284
72	100079_at	0.001385	2191.53	3370.53	Ndufb9	AI845556	NM_023172
73	100095_at	0.000136	524.77	691.5	Scarb1	U37799	NM_016741
74	100576_at	0.003731	211.22	309.87	Pafah1b3	U57746	NM_008776
75	100599_at	0.009874	1611.77	2278.87	Atf4	M94087	NM_009716
76	100628_at	0.004829	1491.4	2766.13	---	AI840263	NM_025523
77	101039_at	0.001053	736.87	1054.37	Col4a2	X04647	NM_009932
78	101063_at	0.000027	220.68	742.23	Tncc	M29793	NM_009393
79	101067_at	0.001669	678.75	840	BC023814	AW124711	NM_026591
80	101094_at	0.001168	189.27	329.87	7420700H20Rik	AI836820	NM_019814
81	101486_at	0.007463	1300.57	1777.63	Psmb10	Y10875	NM_013640
82	101517_at	0.002171	635.12	906.67	Tex261	X81058	NM_009357
83	101989_at	0.000256	2823.92	4891.23	Uqcrc1	AW125380	NM_025407
84	102036_at	0.002657	292.12	421.8 1	810004B07Rik	AW046757	NM_026909
85	102395_at	0.007877	207.67	290.93	Pmp22	Z38110	NM_008885
86	102409_at	0.006707	549.88	743.23	Lsm8	AW046963	NM_133939
87	103074_f_at	0.000346	411.47	747.17	Taf9	AI842969	NM_001015889 /// NM_027139 /// NM_027592 /// XM_620010
88	103631_at	0.004504	231.17	340.3	2810407K09Rik	AA985795	NM_026999
89	103664_r_at	0.008092	318.25	480.6	2810452K22Rik	AA959648	NM_026048
90	103904_at	0.002462	1047.8	2163.97	Krt2-8	X81584	NM_008344
91	103910_at	0.002177	781.53	1028.43	---	AJ249987	NM_020024
92	104366_at	0.000974	473.37	775.9	BC039093	AW047831	XM_131700
93	104573_at	0.000766	480.62	900.4	1110025L05Rik	AA921069	NM_175103
94	104616_g_at	0.005645	541.1	823.47	Il11ra1	M96265	NM_016658
95	104711_at	0.009847	1479.15	1903.13	Vps4a	AW122109	NM_126165
96	104738_at	0.00269	577.62	903.83	Zrf2	D63784	NM_009583 /// NM_009584
97	94347_i_at	0.007505	462.92	569.03	Pcmt1	AW124044	NM_008786
98	94367_at	0.006853	260.5	338.7	AA407809	AI850362	NM_030724
99	94381_at	0.003538	796.53	1165.23	Umpk	L31783	NM_011675
100	95607_at	0.004193	957.28	1272.63	Stard3	X82457	NM_021547
101	96132_at	0.000658	449.45	829.9	AB023957	AB023957	XM_619546
102	96212_at	0.003367	1166.88	1662.3	2310061I04Rik	AI853918	XM_128627
103	96760_at	0.007442	128.9	193.93	Timm10	AW122428	NM_001024853 /// NM_001024854 /// NM_013896
104	96785_at	0.003741	163.88	340.9	0610013D04Rik	AF110520	NM_030697
105	97366_at	0.000839	564.7	734.63	BC026588	AI851024	NM_146075
106	97374_at	0.00401	376.6	576.63	2810025M15Rik	AI840458	NM_027274
107	97424_at	0.00221	1687.9	3393.8	Arl6ip5	AW049647	NM_022992
108	97917_at	0.000656	585.47	762.73	Gcn5l1	Y13778	NM_015740

Table 6

109	97933_at	0.00487	905.57	1149.57	2300006M17Rik	AW045317	XM_127387
110	98031_at	0.001955	801.6	1154.77	Bok	AF027707	NM_016778
111	98429_at	0.006654	1286.02	1897.03	Lypla2	AB009653	NM_011942
112	98492_at	0.00031	485.47	679.93	Cklfsf7	AA920419	NM_133978
113	99032_at	0.002824	80.12	230.33	Rasd1	AF009246	NM_009026
114	99078_at	0.002173	552.62	1022.83	1110033C18Rik	AI839522	NM_133964
115	99444_at	0.003238	280.47	450.93	Ramp2	AJ250490	NM_019444
116	99546_at	0.005569	1984.05	3408.43	Fkbp2	M77831	NM_008020
117	99953_at	0.005011	390.75	574.13	Rgl2	AF100956	NM_009059
118	100007_at	0.007344	1260.93	1654.43	Irf2bp1	AI837573	NM_178757
119	100033_at	0.002557	326.02	484.6	Msh2	X81143	NM_008628
120	100429_at	0.00516	137.55	234.47	---	U89155	NM_008911
121	100446_r_at	0.000197	6419.02	12236.33	Sprr1b	X91825	NM_009265
122	100915_at	0.004564	622.92	966.33	Myh9	AW125698	NM_022410 /// NM_181327
123	100927_at	0.003167	734.27	1398.23	Pltp	U28960	NM_011125
124	100961_at	0.005873	648.83	915.93	Kcnh2	AF012871	NM_013569
125	101408_at	0.008154	397.2	638.37	Gamt	AF010499	NM_010255
126	103273_s_at	0.002904	235.27	362.13	Abcc8	AF037312	NM_011510
127	103524_at	0.005678	265.4	362	Cdan1	AA691078	XM_485054
128	103534_at	0.000053	4886.43	12812.07	---	V00722	NM_016956
129	103935_at	0.00942	334.07	484.47	Atp2a3	AI504474	NM_016745
130	104155_f_at	0.001204	180.1	253.37	Atf3	U19118	NM_007498
131	104408_s_at	0.000173	182.6	345.53	Sox18	L35032	NM_009236
132	92291_f_at	0.000618	47.23	168.37	Cfhl1	M29008	NM_015780
133	92423_at	0.009984	558.88	796.97	Pard6a	AF070970	NM_019695
134	93924_f_at	0.004003	812.72	1145.97	Tuba7	M13443	NM_009449
135	94194_s_at	0.001885	645.6 1	178.5	Hcn2	AJ225122	NM_008226
136	99335_at	0.000285	1501.65	3263.03	Hk1	J05277	NM_010438
137	99842_at	0.001526	259.63	381.73	Col19a1	AB000636	NM_007733
138	100381_at	0.004783	304.98	537.4	Acta1	M12347	NM_009606
139	100718_at	0.00263	1848.65	3298.83	Ptma	X56135	NM_008972
140	102099_f_at	0.008095	1203.68	1708.97	---	AI843637	XM_110121
141	102134_f_at	0.000344	525.12	800.53	Atp5g2	AI461702	NM_026468 /// XM_620687
142	160092_at	0.003749	245.83	561.93	Ifrd1	V00756	NM_013562
143	160195_at	0.000105	1700.3	2244.5	1200013P24Rik	AI846961	NM_029090
144	160212_at	0.00101	327.17	597.93	Ttc4	AW050205	NM_028209
145	160235_at	0.005025	515.9	862.2	5033425B17Rik	AI843521	NM_027215
146	160237_at	0.004904	434.48	749.63	Ndufa6	AW047339	NM_025987

Table 6

147	160305_at	0.004706	419.7	573.8	Psmd11	AW121693	NM_178616
148	160317_at	0.003376	238.85	562.23	Rab34	AI835712	NM_033475
149	160350_at	0.006432	768.5	949.07	Gstz1	AW060750	NM_010363
150	160395_at	0.007084	250.27	429.8	D11Ertd603e	AW046672	NM_026023
151	160431_at	0.000205	468.67	868.7	Mrpl12	AW124432	NM_027204
152	160487_at	0.000167	253.55	601.83	Myl4	M19436	NM_010858
153	160621_at	0.006126	156.38	236.67	Mrps22	AI852322	NM_025485
154	160709_at	0.00982	178.18	237.37	1110001A16Rik	AI788201	---
155	160805_s_at	0.006823	399.22	626.67	Mpdu1	AB025354	NM_011900
156	160869_at	0.006409	512.6	718.2	Sirt3	AI849490	NM_022433
157	160894_at	0.009099	220.35	340.63	Cebpd	X61800	NM_007679
158	161127_i_at	0.007006	305.23	495.13	Rpl24	AV294412	NM_024218 /// XM_194389
159	161145_f_at	0.009011	599.85	821.6	---	AV217314	NM_025313
160	161176_r_at	0.008751	4649.28	6218.03	---	AV230593	NM_013515
161	161327_f_at	0.00102	725.4	1684.3	---	AV104703	NM_011287
162	161487_f_at	0.005352	638.45	891.77	---	AV080542	---
163	161657_f_at	0.003643	1231.48	1755.5	---	AV105022	NM_052835 /// XM_134291 /// XM_486252
164	161715_f_at	0.004661	358.53	464.37	---	AV250651	NM_025667
165	161763_r_at	0.000034	397.82	1719.63	Pip5k2c	AV303514	NM_054097
166	161997_f_at	0.0009	68.98	137.07	---	AV329607	---
167	162457_f_at	0.00009	2992.8	7294.6	---	AV003378	NM_008218
168	106026_at	0.002848	944.8	1465.63	2610318I18Rik	AI845205	NM_145479
169	106196_at	0.0004	435.08	649.8	Htf9c	AW060432	NM_033324
170	106620_at	0.005551	946.32	1503.07	1500019J17Rik	AW120962	NM_026398
171	106659_at	0.005956	288.63	480.2	6720484B16	AI851954	NM_172502
172	107124_at	0.000134	541.67	834.77	2810021O14Rik	AI848296	NM_025480
173	107562_g_at	0.001136	354.67	531.17	2400006N03Rik	AI527865	NM_027186
174	107572_at	0.001189	1208.7	1507.6	Taz	AW046145	NM_181516
175	108020_r_at	0.007103	617.75	1002.3	Hmga1l4	AI850464	NM_023547
176	108473_at	0.00783	390.88	513.6	A730011E05Rik	AA510244	XM_132150
177	108489_at	0.008319	958	1334.47	2810403L02Rik	AW120875	NM_025616
178	108493_at	0.006984	409.03	530.83	Cabc1	AI852390	NM_023341
179	108500_at	0.003436	454.43	660.17	1110001M24Rik	AA792670	---
180	108512_at	0.005691	566.6	890.87	2810038K19Rik	AW125356	NM_023684
181	108564_at	0.007321	361.12	577.67	2310045B01Rik	AA966986	NM_025538
182	108565_at	0.004451	661.5	1006.03	E430002G05Rik	AI853095	NM_173749
183	108586_at	0.006947	289.65	411.77	Psip2	AI842921	NM_133948 /// XM_620422
184	109686_at	0.009172	193.78	275.8	2310040G17Rik	AI122103	NM_183358